BASIC SEX HORMONE THERAPY

ACKNOWLEDGMENTS

Since this publication has achieved a wider acceptance and distribution than was originally intended, we feel bound to point out that other than in presentation, no claim to originality is made. In fact, the work of many research investigators, in endocrine and allied fields, has provided the information contained in these pages.

We are particularly indebted to JÜRGEN FRIEBEL, M.D., of SCHERING A.G., BERLIN, on whose lectures this text is based. To the Medical Research Division of SCHERING A.G , BERLIN, we are also indebted for most of the therapeutic suggestions and the substances that make them possible.

We also express our appreciation to those members of the medical profession, here in Sydney, whose comments and suggestions have been invaluable.

SYDNEY G.P.

BASIC SEX HORMONE THERAPY



SCHERING A. G., BERLIN

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FOREWORD

Originally prepared as a training manual for internal use this book has now been modified with the advice of teachers and consultants in this field to assist those who desire a simple but practical basis on which to study sex hormone therapy. It is therefore brief and in some sections repetition is deliberate for the practical purpose of making each section as complete as possible.

Criticism may be directed at the simplification of what has been thought to be an involved and complex subject, but sex hormone therapy can be readily followed and applied if the basic principles are understood and physiological and pharmacological properties of hormones known. The appropriate sections of this book will, we hope, substantiate this opinion It must be clearly understood that the most difficult step and the pre-requisite for successful therapy is the correct diagnosis This, combined with selection of the appropriate hormone in correct dosage and suitably timed administration, is necessary to provide the desired result. It should be emphasised that hormone therapy is a specific therapy. Random usage, particularly in conditions not related to functional endocrine disturbances, will result in failure Good results will be achieved only when therapy is based on accurate diagnosis.

In each indication an outline or guide to diagnosis is given to make clear the objects and limitations of hormone therapy but diagnosis as such is outside the scope of this book

INTRODUCTION

The classical description of a hormone is given in most dictionaries as that of a chemical substance, or chemical messenger originating in an organ, gland or part, from which it is conveyed through the blood stream to another part of the body, where it exerts its specific effects. As far as sexual endocrinology is concerned, hormones are divided into two main groups, the tropic hormones elaborated by the anterior pituitary and those of the steroid group which are elaborated by the subordinate glands, in particular the gonads

Of the six tropic hormones so far isolated that are secreted by the anterior pituitary, those stimulating the gonads to increased function and secretion are three:

The follicle stimulating hormone (F S H)
The luteinising hormone (L H)
Luteotropic hormone (L T.H.)

Little is currently known regarding the chemical structure of the tropic hormones except that they are basically proteins F S H , since it contains some carbohydrate fraction, is classified as a glycoprotein as also is L H , whereas L T.H. appears to be essentially protein in structure All three are inactivated by certain enzymes

Due to the nature of their structure the gonadotropins have defied chemical synthesis and it is therefore necessary to obtain these substances by extraction from biological sources The availability of human pituitaries imposes severe restrictions in this respect and commercially available gonadotropins are obtained from readier sources such as the blood serum of pregnant mares and human pregnancy urine These "gonadotropin-like" hormones are consequently expensive and do not possess properties identical with those of human pituitary gonadotropins They, nevertheless, have a place in hormone therapy because they provide a method of directly stimulating the subordinate glands

The group of hormones elaborated by the gonads belong to the chemical group known as steroids and are.

The follicle hormone (oestradiol)
The corpus luteum hormone (progesterone)
The testicular hormone (testosterone)

from these spatial formulae. The two formulae differ solely in the nature of the spatial linkage between rings A and B. In formula 3 the substituents (H, CH_3) are situated on the linking carbon atoms 5 and 10 on different sides of the plane of the ring ("trans linkage"). In formula 4 the substituents are situated on the same side which happens to be the front side of the plane of the ring. This pattern of ring linkage is known as the "cis form". Groups of steroid compounds which result from the trans or the cis linkages between rings A and B are described as the allo series (trans) or the normal series (cis).

The radicles are so attached to the carbon atoms that they are directed angularly away from the plane of the steran rings; that is (in the case of steroid hormones), they point towards the viewer.

The substitution of a methyl group at the 13-carbon atom produces a steran derivative—"oestrane" (fig. 5a)—and a further methyl group at the 10-carbon atom results in "androstane" (fig. 5b). If, in addition to the two methyl groups, an ethyl group is attached to the 17-carbon atom, the resultant compound is "pregnane" (fig 5c). These three substances are the basic compounds from which, respectively, all oestrogens, androgens and progestogens are derived (see figs 5d, e, f).

SYSTEMATIC NOMENCLATURE

The names, oestrane, androstane and pregnane, also provide a basis for the "systematic" nomenclature of all sex

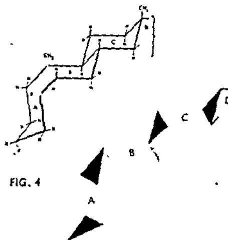
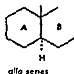
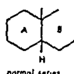
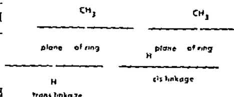


FIG. 4







Cyclopentanoperhydrophenanthrene

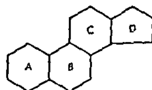


FIG. 1

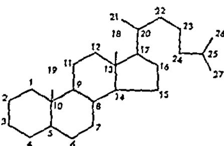


FIG 2

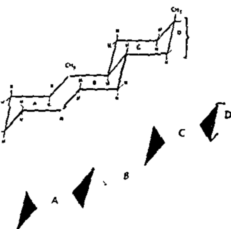


FIG. 3

STEROID CHEMISTRY

In this section the basic facts and terms are set in the roman type and these points should suffice for those who require a working basis for the recognition of terms and structures used in connection with steroid chemistry.

More detailed information is contained in the italicised sections

The basic chemical compound for all steroids is steran. This is a hydrated four-ring system (cyclo-pentano-perhydro-phenanthrene) in which the five-sided carbon ring of cyclopentane is attached to the three six-sided rings *of phenanthrene (fig. 1)*

In representing the structural form of steroids, the hydrogen and carbon symbols are omitted from the rings of the steran nucleus so that structural changes created by the various derivatives may be clearly illustrated and in order to provide a point of reference for such changes as substituted radicles, double bonds, etc, the twenty-seven carbon atoms are numbered (fig. 2)

For further simplicity the structural formulae are depicted in the two dimensions only; as though lying on a flat surface. This serves all practical purposes, but in actual fact the carbon atoms are arranged spatially in two slightly separated parallel planes

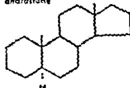
Diagrams 3 and 4 illustrate the two spatial prototypes from which the steroid hormones and their metabolic products are derived. The position of the individual rings and substituents relative to one another can be seen

hormones. By the addition of appropriate suffixes to the basic name, a complete chemical description of a derived compound is obtained. Where, for instance, the compound is "saturated" (i.e., the valencies of each carbon atom are satisfied), the suffix "-ane" is employed. Similarly, "-ene" would indicate that the substance is unsaturated and valencies are satisfied by a double bond, but where more than one double bond is used the suffix accordingly becomes "-diene", "-triene", etc. The symbol Δ also indicates double bonds.

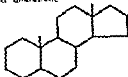
The main substitutions encountered in the steroids involve the hydroxyl groups, which are indicated according to number by "-ol", "-diol", "-triol", etc., or ketone groups denoted by "-one", "-dione", "-trione", etc.

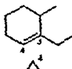
As with other organic compounds, isomers of hormone compounds are encountered; that is, two compounds in which identical groups are attached to identical points of the sterane skeleton. The difference, which may be of importance chemically, since it often leads to one isomer being more active than its counterpart, lies in the spatial direction in which the corresponding substituted groups project from the carbon atom. Those which have the same "configuration" as the radicles of the basic structure (directed toward the viewer) are denoted by "β" in the systematic name and a solid conjoining line in the structural formula. Those directed away from the

androstane

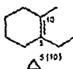


Δ¹ androstene

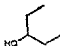




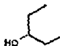
Δ^4



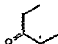
$\Delta^{5(10)}$



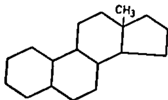
hydroxyl group in the β position



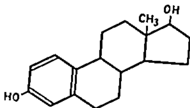
hydroxyl group in the α position



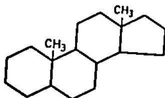
keto group



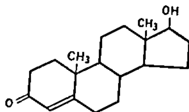
d OESTRANE



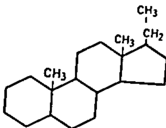
d OESTRADIOL



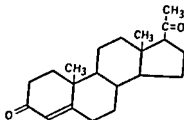
b ANDROSTANE



e TESTOSTERONE



c PREGNANE



f PROGESTERONE

FIG 5

Hydroxy - oxy

Keto - oxo

Hydroxyl substitution is indicated by the prefix "hydroxy" or additional keto groups by the prefix "keto".

Examples:

If a hydroxyl group in the α position is introduced at C-17 on to progesterone this gives 17α-hydroxy-progesterone. If a keto group is introduced at C-11 in androsterone the designation of the molecule then reads: 11-ketoandrosterone.

The expression "oxy" is frequently found for "hydroxy". "Oxo" is now and again encountered as a synonym for "keto"

Desoxy

The absence or removal of a hydroxyl group is expressed by means of the word "desoxy".

Example.

Corticosterone is transformed into 11-desoxycorticosterone by the loss of a hydroxyl group at C-11.

Desoxo

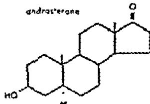
The removal of a keto group is similarly expressed by the word "desoxo".

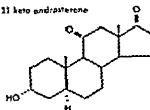
Dihydro - hydro

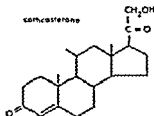
The transformation of a keto group into a hydroxyl group (by the taking up of 2 hydrogen atoms) is signified by the word "dihydro".

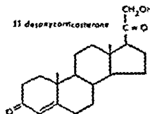
Example:

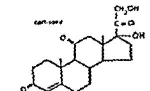
Cortisone, which has a keto group at C-11, is transformed into 11-dihydro-

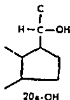


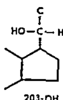


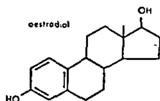


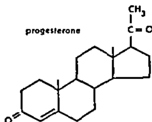


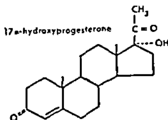












viewer are denoted by "α" and a dotted line.

From the foregoing it can be seen that the systematic name for the substance known commonly as oestradiol—

Δ 1, 3, $5^{(10)}$-oestratriene-3, 17β-diol

would furnish the information that this is an oestrogenic (oestr-ane) substance that is unsaturated and has the valencies satisfied by double bonds (Δ), of which there are three (-triene), each situated between c-atoms 1 and 2, 3 and 4, 5 and 10. There are also two hydroxyl (-diol) groups; one attached to c-atom 3 and the other, which is of β configuration, is attached to c-atom 17.

Although informative, this nomenclature is cumbersome and for practical application each product has a "simple" or "trivial" name based on the group name of the endogenous hormones, as already listed, i e , oestradiol, progesterone and testosterone.

TRIVIAL NOMENCLATURE

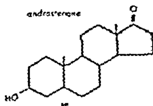
The commercially synthesised steroids retain the simple nomenclature by

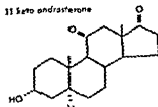
diol and methyl testosterone, or the esters oestradiol benzoate and testosterone propionate. In cases where a trivial name already exists for a given steroid, as is the case for example with all steroid hormones, it is more expedient to employ this instead of the long chemical term.

Hydroxy - oxy
Keto - oxo
Hydroxyl substitution is indicated by the prefix "hydroxy" or additional keto groups by the prefix "keto".

Examples:

If a hydroxyl group in the α position is introduced at C-17 on to progesterone this gives 17α-hydroxy-progesterone.
If a keto group is introduced at C-11 in androsterone the designation of the molecule then reads: 11-ketoandrosterone.
The expression "oxy" is frequently found for "hydroxy". "Oxo" is now and again encountered as a synonym for "keto".



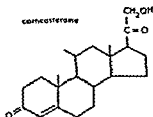


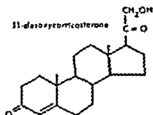
Desoxy

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Example:

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Desoxo

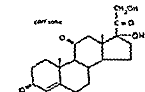
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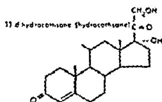
Dihydro - hydro

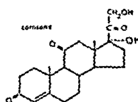
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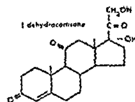
Example:

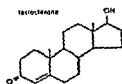
Cortisone, which has a keto group at C-11, is transformed into 11-dihydro-

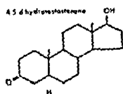


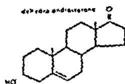












cortisone by the taking up of 2 hydrogen atoms at the keto group. Often however it is simply the expression "hydro" which is used instead of "dihydro" as is the case with hydrocortisone. Similarly, hydrocortisone may be termed "cortisol" to denote the hydroxyl or "ol" group.

Dehydro

The insertion of a double bond is expressed by the word "dehydro".

Example:

A further bond is inserted into cortisone between C-1 and C-2. This changes the compound to 1-dehydrocortisone.
The disappearance of a double bond on the other hand (by adding 2 H atoms) is denoted by the word "dihydro" similarly to the transformation of the keto group into the hydroxyl group.

Example:

Δ^4 double bond of testosterone is transformed by hydrogenation into a single bond. This gives rise to 4, 5-dihydrotestosterone.

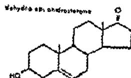
Epi

If an alteration in the configuration of a substituent occurs, i.e. if a substituent which was originally in an α position takes up the β position or vice versa, this is expressed by means of the prefix "epi"

Example

If the spatial position of the 3-hydroxyl group in dehydroandrosterone alters

from the α position to the β position then dehydro-epi-androsterone comes into being.



STEROID GROUPS

The steroids are divided into various groups according to the number of carbon atoms which they contain

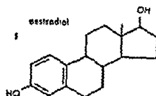
(A) C_{18}-steroids (oestrane derivatives),

(B) C_{19}-steroids (androstane and testane derivatives),

(C) C_{21}-steroids (allopregnane and pregnane derivatives).

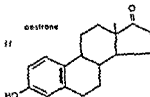
C_{18}-steroids

The C_{18}-steroids are distinguished as oestrane derivatives by the absence of the methyl group at C-10 The most important representatives of this group are the

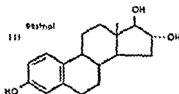


Oestrogens

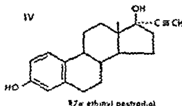
The steroids which belong to this group all possess an aromatic A ring and a hydroxyl group at C-3. The naturally occurring follicular hormone oestradiol (I) occupies the first place as regards activity and practical importance



Oestrone (II) and oestriol (III) are excreted as metabolic products of I in human urine, II is excreted in the form of the sulphuric acid ester, III as the glucuronide II differs from I in that it has a keto group instead of an OH group at C 17, while II has in addition to a hydroxyl group at C-17 an additional OH group in the 16α position Both compounds have a weaker oestrogenic activity than I

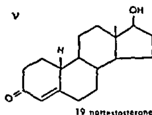


17α ethinyl oestradiol (IV) may be mentioned here as a therapeutically



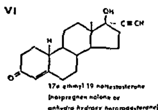
17α ethinyl oestradiol

V



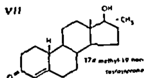
19 nortestosterone

VI



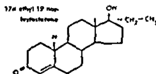
17α ethinyl 19 nortestosterone (norpregnen nolone or anhydro hydroxy norprogesterone)

VII



17α methyl 19 nor-testosterone

VIII



17α ethyl 19 nor-testosterone

valuable substitution product of oestradiol which possesses a powerful oestrogenic action even upon oral administration. The ethinyl group (-C≡CH) is introduced as substituent in the 17α position.

C_{19}-norsteroids

This group of steroids has been very recently developed. Owing to a number of very prominent members it has achieved considerable clinical significance. The term "19-nor" signifies that in these compounds as in the oestrogens, the C-19 methyl group attached to C-10 is absent. The 19-norsteroids differ from the oestrogens however in possessing no aromatic A rings.

19-nortestosterone (V), which is clinically employed in the form of the ester because of its anabolic action, constitutes the parent substance for compounds VI, VII, VIII, while compound IX is derived from the $\Delta^{5(10)}$-isomer of 19-nortestosterone.

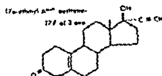
With the exception of 17α-ethyl-19-nortestosterone (VIII) which is used as an anabolic preparation, all 17α-substituted 19-norsteroids included here are used therapeutically because of their powerful progestational action when perorally administered.

The 19-norsteroids have not so far been discovered as naturally occurring compounds They are chemically prepared from oestrogens Very little is yet known about their metabolism

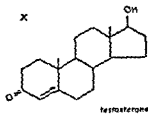
C_{19}-steroids

Testosterone (X), the male sex hormone, and its metabolites represent a great part of this group of steroids

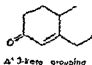
Chemically testosterone is characterised by a hydroxyl group in the β-position at C-17, by a keto group at C-3 and a Δ^4 double bond. This Δ^4-3-keto grouping is present in all other steroid hormones with the exception of the oestrogens.



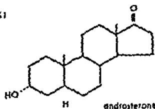
Metabolically, testosterone is converted into the so-called 17-ketosteroids. Besides the oxidation of the 17-hydroxyl group to a ketone, reduction takes place at the 3-keto group to a hydroxyl group, and the Δ^4-double bond is hydrogenised to a single bond. The most important 17-ketosteroids in testosterone metabolism are androsterone (XI) and testane-3α-ol-17-one (XII) which is still usually referred to as aetiocholanolone.

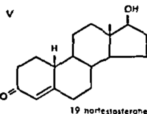


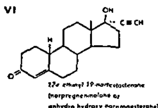
The excretion of XI and XII via the urine proceeds in the form of water soluble sulphates or glucuronides. The two metabolites differ from one another simply in the stereo-relationships at C-5. XI is a representative of the "allo series", while XII belongs to the "normal series".

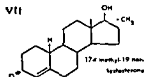


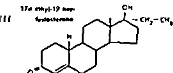
The discovery of 17-ketosteroids with an oxygen function at C-11 on the one hand and the fact on the other hand that 17-ketosteroids are excreted even in the urine of women, led to recognition of the fact that in the metabolism of the adrenocortical hormones, 17-ketosteroids are formed. In man one-third of the 17-ketosteroids found in the urine originate from testosterone metabolism and two-thirds from the adrenal cortex. The most important representatives of the 17-ketosteroids originating from the adrenal cortex











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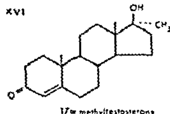
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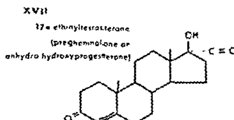
they possess powerful activity even on peroral administration

While 17α-methyltestosterone is principally employed in peroral androgen therapy, 17α-ethinyltestosterone is characterised by progestational activity



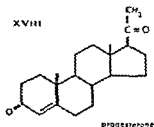
C_{21}-steroids

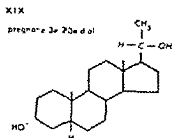
The compounds summarised in this group numerically far exceed the steroid bodies contained in the previously discussed groups Progesterone and its derivatives as well as adreno cortical hormones belong to this group



Progesterone and its derivatives

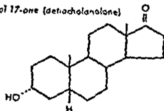
The progesterone (XVIII) formed in the corpora lutea of the ovary is the second female sex hormone Chemically, progesterone is derived from pregnane and is characterised chemically by the Δ^4-3 keto grouping together with a further keto group at C-20 In addition to its occurrence in the corpus luteum it is formed also in the adrenal cortex and constitutes an intermediate product in the biosynthesis of the adrenocortical hormones During metabolism XVIII undergoes reduction The Δ^4-double bond disappears and the keto groups are reduced to hydroxyl groups Pregnane 3α, 20α-diol (XIX) results and is excreted in the urine in the glucuronide form The pregnanediol determination allows important conclusions to be made as regards the function of the corpus luteum in the woman Progesterone and 17α ethinyl testosterone were for a long time the only progesta



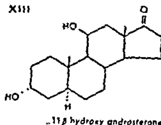


XII

testone 3α ol 17-one (aetiocholanolone)

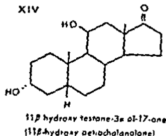


XIII



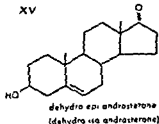
11β hydroxy androsterone

XIV



11β hydroxy testone-3α ol-17-one (11β-hydroxy aetiocholanolone)

XV



dehydro epi androsterone (dehydro iso androsterone)

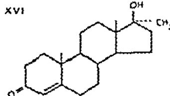
are 11β-hydroxy-androsterone (XIII), 11β-hydroxy-testane-3α-ol-17-one (11β-hydroxy-aetiocholanolone) (XIV) and dehydro-epi-androsterone (XV).

Compounds XIII and XIV, like the testosterone metabolites XI and XII mentioned above, possess a saturated A ring and a hydroxyl group in the α position at C-3, while dehydro-epi-androsterone exhibits a 3-hydroxyl group in the β position. (XV is still frequently designated as dehydro iso-androsterone.)

The determination of the 17-ketosteroids in the urine in many cases permits diagnostic conclusions to be made as regards function and affections of the gonads and adrenal cortex, especially when the individual steroids are separated by special methods and estimated individually. A further two substitutive products of testosterone are of interest because of their therapeutic application: 17α-methyl-testosterone (XVI) and 17α-ethinyl-testosterone (XVII).

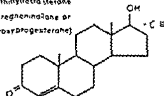
In both compounds the 17-hydroxyl group in the 17α position becomes tertiary by the insertion of a radical (methyl or ethinyl group), i.e. the OH group is on a C-atom whose remaining three valencies are attached to other C-atoms. In contrast to the secondary hydroxyl group, such as is possessed by testosterone for example, the OH group so formed is no longer oxidisable to the 17 ketone. Consequently these compounds resist oxidative inactivation processes in the body and as a result of this property

they possess powerful activity even on peroral administration.
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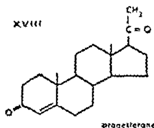
C_{21}-steroids

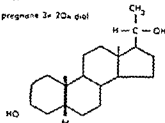
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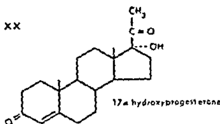


Progesterone and its derivatives

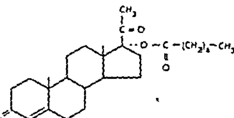
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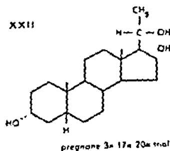




17α hydroxyprogesterone



17α hydroxyprogesterone 17 capronate



pregnane 3α 17α 20α triol

tionally active substances known. In more recent times however a whole series of progestational steroids has been synthesised. Of the compounds employed clinically 17α-hydroxy-progesterone-17-capronate (XXI) should be mentioned. It possesses a powerful and protracted progestational action In this connection it is interesting to note that the free 17α-hydroxy-progesterone is practically inert and only becomes a progestogen through esterification (XX) occupies a key position in the biosynthesis of the adrenocortical hormones and is transformed into glucocorticoids by means of hydroxylating enzymes acting at C-21 and C-11 The reduction and excretion product of XX is pregnane-3α, 17α, 20α-triol (XXII) This is excreted in the urine in increased amounts in disturbances of the hydroxylation processes in the adrenal cortex Its determination furnishes valuable diagnostic information in disturbances of the adrenal cortex

The naturally occurring steroids and their metabolites, whether extracted or chemically synthesised, are generally inactive when given by mouth and relatively weak in action by modern standards Advances in commercial research and production have now provided a variety of forms by which steroid hormones may be simply and effectively applied There are potent oral oestrogens and progestogens There are long acting intramuscular depot forms of individual steroids with an action particularly suited for therapy related to the menstrual cycle as well as for long term maintenance therapy

THE ENDOCRINE GLANDS OF THE REPRODUCTIVE SYSTEM

Endocrine glands are ductless glands which pour their secretions (hormones) directly into the blood stream, which transports them to various sites in the body where they exert their specific actions.

THE PITUITARY

The pituitary gland, although not the controlling centre, can be regarded as the controlling gland in the endocrine system. This small body is situated within a cavity (sella turcica) of the sphenoid bone which forms the floor of the cranium. Anatomically the pituitary is divided into three lobes, the anterior lobe (pars anterior) and the posterior lobe (pars nervosa), which are separated by an intermediate lobe (pars intermedia) These three lobes are connected to the third ventricle of the brain by a short stalk known as the infundibulum The pituitary gland is also known as the hypophysis cerebri and in terms of this description can be subdivided into two major sections

(a) adenohypophysis,

(b) neurohypophysis

The adenohypophysis includes the anterior lobe and the intermediate lobe and is derived from the ectoderm of primitive oral tissues and consequently is glandular and capable of secretion. The major cells of the adenophypophysis are chromophobes which give rise to a series of chromophils Two of these are of principal importance in endocrine secretion, namely the acidophils or α cells and the basophils or β cells. It is thought that the acidophils are responsible for the production of L H and L T.H and the basophils for the production of F.S H

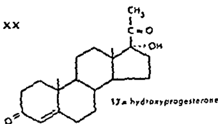
The neurohypophysis is constituted by the posterior lobe and the infundibulum and is comprised of neural elements derived from a downward growth of these elements from the hypothalamus The major cells are pituicytes containing secretory granules.

THE PITUITARY HORMONES

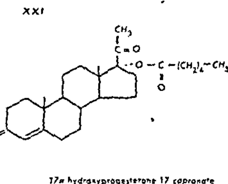
Anterior Lobe

The secretions of the pars anterior of the pituitary are known as tropic hormones and act directly upon subordinate endocrine

XX

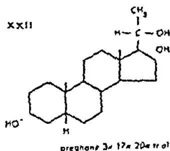


XXI



17α hydroxyprogesterone 17 capronate

XXII



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glands to stimulate in turn the production of steroid hormones Numerous tropic factors may be assumed to arise from the anterior pituitary, such as ketogenic, diabetogenic, glycotropic and parathyrotropic factors but such substances have not as yet been isolated. The tropic hormones of the anterior pituitary which have been extracted, identified and applied to clinical medicine are:

growth hormone

thyrotropic hormone

which stimulates the thyroid gland to the production of thyroxin

adrenocorticotropic hormone (A C.T.H)

which stimulates the production from the adrenal cortex of glucocorticoids, androgens, oestrogens and progestogens

gonadotropic hormones

which initiate and regulate either spermatogenesis or follicular maturation and ovulation as well as stimulate gonadal production of androgens or oestrogens and progestogens

prolactin

the lactogenic hormone, which is assumed to be responsible for initiation and possibly the maintenance of milk secretion and is regarded as being identical with growth hormone, rather than gonadotropins, in many species

Posterior Lobe

The hormones secreted by the posterior lobe are·

Oxytocin—which stimulates uterine contraction and which initiates the muscular spasms leading to childbirth. Oxytocin also appears to be associated with the milk ejection reflex (draft reflex)

Vasopressin—or antidiuretic hormone (A D H) which stimulates muscular contraction in the intestinal tracts, acts upon arterial smooth muscles to raise blood pressure and possesses an antidiuretic action leading to the diminution of urinary output Vasopressin also has some slight oxytocin action


PITUITARY GLAND
PARS NERVOSA
OXYTOCIN
VASOPRESSIN
ANTIDIURETIN
PARS INTERMEDIA
INTERMEDIN
MELANIN
THYROTROPIN
THYROXIN
PARS ANTERIOR
SOMATOTROPIN
ADRENO CORTICOTROPIN
A C T H
CORTICOIDS
OESTROGENS
ANDROGENS
PROGESTOGENS
GONADOTROPINS
GROWTH
GAMETOGENIC HORMONE
INTERSTITIAL CELL STIMULATING HORMONE
FOLLICLE STIMULATING HORMONE
LUTEINISING HORMONE
LUTEOTROPIC HORMONE
SPERMATOGENESIS
TESTOSTERONE
OESTRADIOL
OVULATION
PROGESTERONE

FIG 6

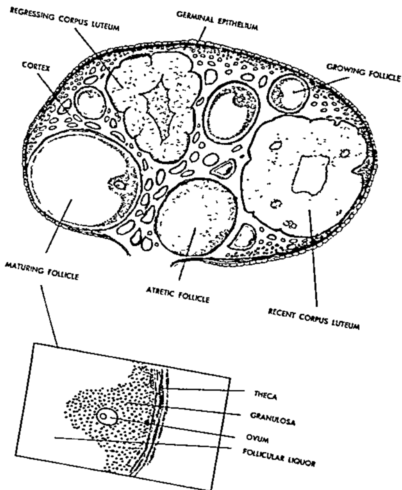


FIG 7

THE OVARY

THE OVARIES

The human ovaries are oval organs approximately 30 mm. long by 15 mm. wide and 10 mm. thick, weighing about 5 gm (see fig. 7). The central portion of the ovary (medulla) consists of a highly vascular fibrous stroma which is the homologue of the male germinal tissue and under certain abnormal conditions may be associated with the increased production of male hormone (see Androgens in the Female, p. 40)

Surrounding the medulla is a thick cortex of cells and fibres and both cortex and medulla are enclosed within a dense tunic of fibrous tissues (tunica albuginea). The external surface of the tunic is covered by a layer of germinal epithelium. The section of the cortex which lies beneath this tunic may contain up to 700,000 primordial follicles in each ovary at the time of birth, but these vast numbers are rapidly reduced by unknown factors and by the time of puberty approximately 300,000 per ovary remain A further subsequent reduction takes place over remaining years and at 45 years some 8,000 exist in each ovary. During the sexually mature span only some 300-400 primordial follicles will be liberated as mature ovum. From puberty numbers of primary follicles undergo development at regular intervals In each cycle an average of eight follicles will mature with one follicle undergoing much more rapid development than the remainder

The ovum enlarges, the cells surrounding it thicken to form layers and secrete a liquid (follicular liquor) and numerous small pools (Call-Exner bodies) coalesce to form an antrum enclosed by the granulosa cells. The resultant vesicle is known as a Graafian follicle. The ovum becomes embedded in a mass of granulosa cells which now form the internal lining of the follicle and the connective tissue of the cortex surrounding the follicle forms two layers (theca externa and theca interna) It is from the cells of the theca interna that the follicular hormone (oestradiol) is secreted

As it approaches maturity the Graafian follicle migrates towards the periphery of the ovary. The tunica albuginea becomes distended and eventually ruptures with simultaneous rupture of the follicle The follicular liquor is discharged into the peritoneal cavity carrying with it the ovum and its corona radiata of granulosa cells Once the rupture has taken place, a blood clot

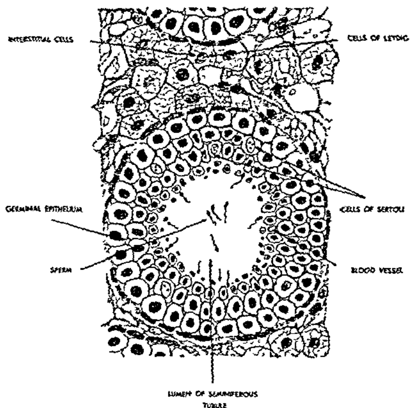


FIG. 8

THE TESTICULAR TISSUES

forms (corpus haemorrhagica) and transformation of the remaining granulosa and theca cells takes place There is rapid division and hypertrophy of the cells giving rise to a greyish red structure in which carotene subsequently appears imparting the yellow colour that gives the name of corpus luteum to these tissues It is from the cells of the corpus luteum that progesterone is liberated.

The corpus luteum eventually regresses (depending on whether or not pregnancy ensues) to become the corpus albicans and ultimately a small scar The many follicles that fail to mature and liberate an ovum undergo atresia and are absorbed

THE TESTES

In the human the testes are oval organs approximately 5 cm. x 3 cm. x 2 cm., and weighing about 25 gm. From the third month of embryonic life they start a descent down through the inguinal ring to the scrotum

Each testis, within its tunic of connective and fibrous tissue, is composed of hundreds of minute seminiferous tubules, each 60 to 100 cm in length, interspersed in interstitial tissue The walls of the tubules are lined with several layers of germinal epithelium (see fig 8), which give rise to the formation of sperm by undergoing successive stages of spermatogenesis, i e, from spermatogonia to spermatocytes to spermatids to spermatozoa

Also present in the seminiferous tubules are cells (Sertoli cells), the function of which is not clear, but it is thought that they are homologous to the granulosa cells of the ovary.

Distributed in clumps in the loose connective tissue between the tubules are large irregular cells (interstitial cells or cells of Leydig), and it is these cells that elaborate the male hormone, testosterone

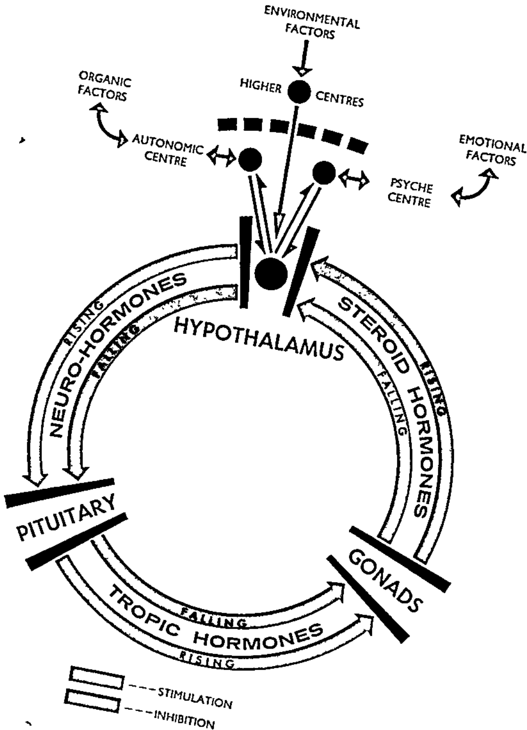

ENVIRONMENTAL FACTORS
HIGHER CENTRES
ORGANIC FACTORS
AUTONOMIC CENTRE
EMOTIONAL FACTORS
PSYCHE CENTRE
RISING
NEURO-HORMONES
FALLING
HYPOTHALAMUS
STEROID HORMONES
RISING
FALLING
PITUITARY
GONADS
TROPIC HORMONES
FALLING
RISING
STIMULATION
INHIBITION

FIG 9

CONTROL OF ENDOCRINE FUNCTION

DIENCEPHALON

The diencephalon or the third ventricle of the brain consists of three major subdivisions:

(a) *Epithalamus* or roof

(b) Thalamus—which comprises the lateral wall together with an intermediate connection (massa intermedia)

(c) Hypothalamus—which comprises the floor of the third ventricle together with part of the lateral walls.

The hypothalamus is the controlling centre of endocrine function throughout the body. It also exerts a major control over the autonomic nervous system and regulates all basic body rhythms. It is closely connected with the centre of psyche and is responsible for the integration of emotional expression with behavioural pattern. By virtue of its linkage with all aspects of the cerebral cortex it is responsible for the physiological reaction of the organism to environmental factors. The hypothalamus is connected to the pituitary gland by a portal blood system and also by nerve fibres to the posterior lobe of the pituitary and to a lesser extent the anterior lobe. Its control over the endocrine system can therefore be exerted either by direct nervous impulse or by the release of neurohormones into the common portal blood system

The activity of the hypothalamus in controlling the endocrine system is governed principally by chemo receptors which are sensitive to blood levels of hormones secreted by subordinate endocrine glands. The production of the stimulating tropic hormone is suppressed when the peripheral hormones reach a threshold blood level. Conversely this inhibition is released when circulating steroid levels fall below a certain threshold level By this mechanism a state of equilibrium, which answers the demands of the particular circumstances, is provided (see fig 9). As a result of this mechanism it follows that steroid secretion is a self limiting process Similarly the exogenous administration of a steroid in appropriate amounts may be expected to reduce endogenous production There is, however, positive evidence* that such suppression, when withdrawn, leads to sub

* Haller 7th International Conference on Planned Parenthood Singapore, 1963

HORMONES OF THE REPRODUCTIVE SYSTEM

GONADOTROPIC HORMONES

It is generally accepted that three gonadotropic factors are elaborated by the anterior pituitary and since human F.S H. has been isolated in a relatively pure form, it must be accepted that at least two separate gonadotropic entities exist The actual site of production of gonadotropins is not established but it is thought that the acidophils and basophils are responsible. The normal range of amounts produced, as measured in the urine, is 3-34 Human Menopausal Gonadotropin units per 24 hours with a mean value of 10 H.M.G. units. In post-menopausal women, however, the range is 35-158 H.M.G. units with a mean of 56.

Gonadotropins are identical in both the male and female organism, but the tissues they stimulate differ in each sex; therefore they are named according to their specific physiological role

In the Female

Follicle Stimulating Hormone (F.S H.)

F.S.H. acts upon the primordial follicles of the ovary to stimulate ripening and maturation of the Graafian follicle

F.S H. stimulates the theca interna cells of the Graafian follicle to secrete the follicular hormone oestradiol.

Luteinising Hormone (L.H.)

L H. is responsible for rupture of the Graafian follicle, the formation of the corpus luteum from the remnants of the Graafian follicle and initial secretion of progesterone in the cycle.

The high level of L.H. appearing immediately prior to ovulation combining with small amounts of F.S H causes rupture of the follicle and release of the ovum L.H. is then responsible for the development of the corpus luteum (yellow body) from the (theca cell) remnants of the Graafian follicle It is also generally considered that L H stimulates the initial secretion of the corpus luteum hormone, progesterone

Luteotropic Hormone (L.T.H.)

Although the position is not entirely clear, it has been presumed that the action of L.H on the follicle ceases with the formation of the corpus luteum The presence of a third factor (L T.H)

sequent increased output via increased pituitary stimulus (rebound effect). It has also been postulated that, when gonadotropins are suppressed, andrenocorticotropic hormone secretion is proportionally increased and vice versa (anterior pituitary shift). There seems to be no doubt that when A C.T.H has been produced in excess, gonadotropin secretion is suppressed and there is good evidence to show that the converse also applies.† The interplay which provides for requirements of a regular, ovulatory menstrual cycle is discussed on p. 49.

By virtue of its close relation to other aspects mentioned before, the activity of the hypothalamus is also subject to the influence *of physiological or environmental and emotional factors.*

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† Butt, Crooke *et al.*, *J Obst. & Gynae Brit. Comm.*, 70 604 (1963)

HORMONES OF THE REPRODUCTIVE SYSTEM

GONADOTROPIC HORMONES

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Although the position is not entirely clear, it has been presumed that the action of L.H. on the follicle ceases with the formation of the corpus luteum. The presence of a third factor (L.T.H.)

is generally accepted as being responsible for the continued secretory function of the corpus luteum. This factor is no longer accepted as being identical with Prolactin but further work will be necessary to confirm its presence as a separate entity to L H.

In the Male

Gametogenic Hormone

In the male, F.S.H. is given the name of gametogenic hormone. It is responsible for spermatogenesis by stimulation of the germinal epithelium of the seminiferous tubules.

Interstitial Cell Stimulating Hormone (I.C.S.H)

This is the luteinising hormone and is responsible for the secretion of testosterone from the interstitial (Leydig) cells of the testes.

As mentioned in the introductory section, the gonadotropic hormones are complex proteo-hormones, the chemistry of which is as yet unknown. While it is possible to extract certain factors in a relatively pure form from a human source, the scant availability of human pituitaries precludes any commercial application. Apart from the growth hormone it would appear that these substances are not species specific. Consequently the commercially available hormones in this group are produced by extraction from biological material and are standardised in units of biological activity, i.e International Units (I U)

Serum Gonadotropin (P.M S)—Primantron (Schering A G)—is extracted from the blood serum of pregnant mares. This substance does not appear to be produced by the pituitary of the mare and there is evidence that it is placental in origin It does, however, have a follicle stimulating action similar to the true follicle stimulating hormone of the human (F S H) The similarity in effect is not sufficient to produce clinical results equal to those obtained with human F S H. but there is currently no commercially available alternative substance Because it is obtained from a non-human source, P.M S. may be treated as a foreign protein in the body and an "anti hormone" production may be stimulated by continuous use Therefore this hormone is usually administered in courses of not more than three weeks duration with an interval of three weeks between each course It is not definite that the protein nature of the P.M.S itself pro

motes this anti-body reaction and it is possible that other protein moieties contained in such extracts may be the cause.

Human Chorionic Gonadotropin (H.C.G.)—Primogonyl (Schering A.G.)—is extracted from human pregnancy urine where it appears in quite large quantities during the first trimester. Chorionic gonadotropin, while presumably not identical with pituitary L.H. and L.T.H. factors, is strongly luteinising in its action and may be successfully used to reproduce the effects of its pituitary counter part. By virtue of its human origin no "anti-hormone" effect need be expected from its administration.

Both P.M.S. and H.C.G. by virtue of their protein composition are inactivated by digestive processes. Consequently they must be administered parenterally.

GONADAL HORMONES

As adequately illustrated in the introduction, the gonadal hormones are steroids, the chemistry of which is well known since they are all derivatives of the basic steran nucleus, cyclo pentano-perhydro phenanthrene.

Derivatives of steroid hormones are commercially available in a wide range of presentations for parenteral, oral and transcutaneous administration. Their effects are well defined, activity and presentation are standardised in weight of substance, and dosages are given by weight, in milligrams.

Oestrogens in the Female

Production

The main source of oestrogen produced in the body is from the theca interna cells of the Graafian follicle as it matures under the influence of F.S.H. This oestrogen is called follicular hormone and is chemically identified as oestradiol. The total amount produced thus is approximately 10 mg. per cycle.

Other sources of oestrogen production are the corpus luteum and the cortex of the adrenal gland. Amounts from adrenal sites would be small by comparison to ovarian production, but during pregnancy the placenta produces oestrogen in amounts that increase to about a thousand times the normal production.

Excretion

Oestrogen is excreted principally via the kidney either unchanged as oestradiol or as oestrone, oestriol and lesser metabolites but a small proportion is excreted in the bile following degradation in the liver (see Assays, p 68). It is interesting to note that oestrogens are more difficult to degrade than other steroid hormones and it is not unusual for gynaecomastia, uterine bleedings and other signs of hyperoestrinism to follow liver damage.

Action: The action of sex hormones in the body is best considered under three headings:

Genital effects

Extragenital effects

Effects with other hormones

Since it is felt that these effects are the basis of all hormone therapies and should be committed to memory, numbered headings are used in the subsequent sections to facilitate this

Genital Effects of Oestrogens

1 *Growth Effect of Oestrogen*—Oestrogen is responsible for stimulation of growth and the maintenance of mature sexual development in the—

- Ovaries (where it increases weight and the response to gonadotropins),
- Uterus and cervix (particularly uterine growth during pregnancy),
- Fallopian tubes;
- Vagina,
- External genitalia,
- Breasts (with proliferation of the glandular and duct tissue and pigmentation of the nipple)

2 *Proliferative Effect of Oestrogen*—Oestrogen exerts a pronounced effect on all tissues arising from the Mullerian duct system.

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partic.

A. *Endometrium* (see p. 51)

B. *Vaginal Epithelium* (see p. 55)

C. *Fallopian Tubes* (see p. 55)

D. *Endocervix* (see p. 51)

Extragenital Effects of Oestrogens

1. *Secondary Sex Characteristics*—Oestrogen is responsible for general development and maintenance of such development in:

Fat deposition on breasts and hips, giving the typical female contours,

Limitation of pubic hair to the typical inverted triangular shape;

Vocal cord development to provide the higher pitch and lighter timbre,

Psyche formation,

Skin texture of a soft, fine and non-greasy type;

General hair growth and texture.

2. *Protein Anabolic Effect*—This is particularly strong in bone and in conjunction with (3) hastens closure of the epiphyses

3. *Mineral Retention Effect*—The retention of calcium, sodium and phosphorus. In this effect the retention of sodium leads to a corresponding retention of water.

4. *Inhibition of Pituitary*—This effect, which is particularly strong with oestrogens, plays a major role in the functional relationship between pituitary and ovaries and is consequently employed in a number of therapeutic applications

5. *Vasodilatory Effect*—Stimulation of peripheral circulation

6. *Psyche Stimulation*—Stimulation of a general feeling of well-being

7. *General Proliferative Effect*—Proliferation and re-epithelisation of epithelial tissues which is particularly marked in nasal and buccal mucosa

8. *Styptic Effect* on uterine haemorrhage.

Effects with Other Hormones

Androgens

(a) Oestrogens are synergistic with androgens in all the extra-genital effects of both hormones, excluding the secondary sex characteristics.

(b) Oestrogens are antagonistic to androgens in all genital effects in the female.

Progestogens

(a) Oestrogen in small amounts ensures the full effectiveness of progesterone; whilst large amounts may be antagonistic to progesterone

(b) Oestrogen may be antagonised by progesterone.

Pituitary Gonadotropins

(a) Oestrogen (in any amount) inhibits F.S H.

(b) Rising levels of oestrogen stimulate L.H. and L T H. production.

(c) High levels of oestrogen inhibit L H and L T H production.

Progestogens

Production

There are several sources of progestogen production. During the normal cycle it stems mainly from the corpus luteum which has formed from the ruptured follicle under the influence of L H, and this progestogen is known as the corpus luteum hormone, or chemically, as progesterone It does not appear in the cycle in significant amounts, therefore, until and unless ovulation has taken place, but due to production from the adrenal cortex the presence of small amounts throughout the entire cycle is independent of the formation of a corpus luteum. Normal output by the corpus luteum reaches a maximum of 50 mg daily and is approximately 250 mg per cycle, but due to placental production during pregnancy this level rises tenfold

Excretion

Following degradation by the liver, progesterone is excreted in the urine mainly as pregnanediol (see Assays, p 66) However, it must be remembered that not all progestogens are excreted as pregnanediol

Genital Effects of Progestogens

1. *Secretory Effect*—Progesterone produces pronounced changes both in appearance and activity of tissues derived from the Mullerian duct system which have previously been "primed" or proliferated by the effect of oestrogen.

A. *Endometrium* (see p. 51)

B. *Vaginal Epithelium* (see p. 55)

C. *Endocervix* (see p. 54)

2. *Maintenance of Pregnancy*—Progesterone plays an essential role in establishing a thick layer of tissues richly supplied with blood and glycogen, providing ideal conditions for the nidation of a fertilised ovum and the sustenance of that ovum until such time as complete nidation allows for maternal nourishment. That progesterone is essential for the initial establishment and the continuation of pregnancy has been demonstrated by the classical experiments of Corner and Allen.*

3. *Sedation of Uterine Muscle*—Presence of adequate levels of progesterone would also appear to be essential for the continued maintenance of advancing pregnancy. Progesterone has been shown to have a profound effect on the myometrium in keeping with its major role in the maintenance of pregnancy. Csapo† has demonstrated that progesterone, possibly by altering the permeability of the membrane, influences the sodium, potassium and calcium content of the cell and that this effect, without altering the final system of contracture, abolishes the conduction of stimuli and also any reactivity to outside stimuli. Amongst other effects it reduces excitability and limits the development of tension in the myometrium.

4. *Breast Development*—Progesterone acts with oestrogen to develop ducts and alveoli, and its presence is essential for lactation.

5. *A Styptic Effect on Uterine Haemorrhage*—This is non-specific and weaker than oestrogen.

Extragenital Effects of Progestogens

1. *Thermogenic Effect*—The presence of progesterone results in an elevation of the basal body temperature and this serves as a

* Corner. *Amer. J. Physiol.* 86 74 (1928)

† Csapo. *Rec. Prog. Hormone Research* 12 405 (1956)

simple and precise means of assessing the occurrence of ovulation and very approximately the level of progesterone in the cycle. This elevation in body temperature is recorded daily and the basal body temperature should show a sustained rise of 0·8 to 1° F. after ovulation (see p. 63).

2. *Water Excretion*—Animal experiments have shown that progesterone promotes water excretion possibly by means of an anti-aldosterone effect.

Effects with Other Hormones

Oestrogens

(a) Progesterone is dependent on the presence of oestrogen for its full effect, but is antagonised by large amounts of oestrogen

(b) Progesterone in high dosage antagonises oestrogen.

Androgens

Progesterone is broadly synergistic to androgens in the genital effects of progesterone on vaginal smears and to an extent on the endometrium

Pituitary Gonadotropins

Progesterone is a relatively weak inhibitor of the anterior pituitary, but this does not apply to all progestogens. The norsteroids such as norethisterone have a strong action in this regard.

Androgens in the Female

Production

The site of androgen production in the female is the adrenal cortex The level of androgens produced by the adrenal cortex is approximately a half to two-thirds of the total male output, and it is reasonable therefore to consider androgen administration in the female as not unphysiological However, with the introduction of the norsteroids many androgen therapies can be replaced by progestogens

Excretion

Degradation is by the liver, and excretion is in the form of 17 ketosteroids in the urine (see Assays, p 68) The average excretion level of 17-ketosteroids in the female is about 7 mg per 24 hours urine.

In some conditions arising from excessive androgen production, e.g. arrhenoblastoma, a normal 17-ketosteroid excretion is sometimes found. This variation may be explained by the fact that the biological activity of the androgen so produced may be sufficient to produce physical changes in amounts too small to influence total excretion.

Genital Effects

1. Limitation of the proliferative effects of oestrogen on the breast, endometrium, vaginal epithelium, etc.

2. Limitation of the growth effects of oestrogen in the uterus, and other genitalia.

3 Stimulation of clitoral growth and sensitivity.

4 Stimulation of libido.

Extragenital Effects

1 *Growth of pubic and axillary hair.*

2 *Protein anabolic effect,* which is particularly strong in muscle as well as bone tissues.

3 *Mineral retention effect,* notably in the bones giving retention of calcium, sodium and phosphorus As with oestrogens the retention of sodium is accompanied by water retention but to a lesser degree.

4. *Inhibition of pituitary* which is more marked than that of progesterone but not equal to that of oestrogen

5 *Vasodilatory effect,* principally on peripheral tissues

6. *Psyche stimulation* in which effect androgens are very much stronger than oestrogens.

7 *Styptic effect* on uterine haemorrhage

Effects with Other Hormones

1 Antagonistic to oestrogen in genital effects

2 Synergistic to oestrogen in extragenital effects, except for secondary sexual development

3. Broadly synergistic to progesterone in its effect on vaginal and endometrial tissues.

4 Inhibits F S H and L H and L T.H

Effects of Excessive Androgens

Under certain conditions, when androgens are present in elevated levels, the normal effects may become exaggerated and produce undesirable defeminising results which may be broadly classified as "virilising syndromes". These may arise from such causative factors as:

1. *Iatrogenic*—as a result of excessive androgen or corticoid administration. There is no unanimity as to the level of administration that is liable to produce undesirable effects. It has been generally accepted that dosages equivalent to 300 mg. of testosterone proprionate per cycle constitute a virilising threshold. However, there appear to be marked individual variations.

2. *Congenital*—as a result of adrenal hyperplasia (adrenogenital syndrome). Congenital virilising syndromes may also arise from disturbances of maternal androgen production or metabolism or as a result of androgens and other steroids administered to the mother.

3. *Adrenal hyperplasia and adrenal tumours*—either of these two entities may result in an excessive production of adrenal androgen. Where this is accompanied by excessive corticoid production the clinical picture of Cushing's syndrome may result. Increased adrenal androgens are reflected in raised 17-ketosteroid excretion but in virilising adrenal hyperplasia this increase may be suppressed with corticosteroids whereas with adrenal tumour the use of corticosteroids produces little, if any, effect.

4. *Stein-Leventhal syndrome*—In this syndrome the association of enlarged polycystic ovaries with virilisation has suggested the ovaries as a possible site of androgen production. It is possible, however, that the androgenic symptoms which arise may be secondary to adrenal hyperfunction. Surgical measures (wedge resection), while providing correction of ovarian dysfunction, do not appear to give any remission from abnormal androgenic effects.

5. *Ovarian Tumours*—Masculinising effects also accompany certain rare forms of ovarian tumours, such as arrhenoblastoma, which are capable of producing androgens. As is the case in Stein-Leventhal syndrome the 17-ketosteroid excretion is variable and may appear normal or may be consistently elevated.

6. *Idiopathic*—In a number of women signs of androgenic activity may appear at a clinical level, usually in the form of facial hirsuties, without any discernible alteration in endocrine production. Allowing for individual and racial variations in body hair distribution and for the fact that increased facial hair growth usually follows the menopause, such cases can be classified as idiopathic and at present no treatment, other than cosmetic control, is available.

The term virilisation as applied to these syndromes is broad and covers many features principally related to genital effects. Several or many of these may be recognisable and the degree might vary from mild to severe, according to the severity of the causative stimulus The more common signs are

Virilisation—Hirsutism of face and body—Acne arising from increased sebaceous gland activity combined with staphylococcal infection—Hair distribution variations toward male pubic hair and scalp hair pattern—Psyche changes involving the development of male psyche characteristics—Clitoral enlargement and increased libido—Loss of menstruation—Vocal changes In more severe cases regression of the genitalia, alteration of fat distribution and increased musculature may be involved

It is also reasonable to expect that the extragenital effects of androgens will be similarly exaggerated, and an undesirable effect which may be manifested as a result is oedema associated with sodium retention.

All these effects are reversible and disappear soon after the excessive androgen production or administration is reduced with the exception of vocal changes Shortening and thickening of the vocal chords may lower the pitch to the extent of an octave or more and this may be permanent depending on the duration and degree of excessive androgen levels

Androgens in the Male

Production

There are two sources of androgen in the male. One is the cortex of the adrenal glands which produce half to two-thirds of the total amount, as estimated in the urine excretion of 17-ketosteroids The other source is the interstitial cells (cells of Leydig) in the testes

Excretion

Degradation is by the liver, and excretion in the urine is in the form of 17-ketosteroids. The average excretion level is 15 mg per 24 hours urine (see Assays, p. 68).

Genital Effects

1. *Growth effect*—Stimulating the growth and maintenance of mature development of the penis, scrotum, chord, testes, prostate, seminal vesicle.
2. *Nutrition factor in spermatogenesis*—Fructose production in testes and prostatic secretions.
3. *Libido effect*—increasing the sexual appetite

Extragenital Effects

1. *Secondary sex characteristics*—Voice, beard, pubic hair distribution, scalp hair distribution, psyche, heavy musculature etc.
2. *Protein anabolic effect.*
3. *Psyche stimulation*—stronger than oestrogens.
4. *Mineral retention*—of calcium, phosphorus, etc.
5. *Peripheral circulatory stimulation*—weaker than oestrogen
6. *Inhibition of pituitary*—weaker than oestrogen
7. *Strengthening of musculature*, urinary bladder, sphincters
8. *Nephrotrophic effect* (increase weight of kidney).
9. *Glycogen metabolism in heart muscle.*

Effects with Other Hormones

1. Antagonistic to oestrogen in genital effects
2. Synergistic to oestrogen in extragenital effects except secondary sex characteristics
3. Inhibits I.C.S.H. and Gametogenic Hormone

Oestrogen in the Male

Production

The sites of oestrogen production in the male are the testes and the adrenal cortex. Oestrogen production in the testes is well-

known from animal experiments and in some animals, e.g., the horse, the oestrogen level in the male is extremely high

Excretion

After degradation by the liver, excretion is via the bile and the urine (see Assays, p 68)

Genital Effects

1. *Growth effect*—Breast, prostate, seminal vesicle and vas deferens respond to the growth effect of oestrogen The glandular and duct tissue of the male breast and the interstitial tissue of the prostate respond quickly to high dosage oestrogen therapy by growth

2 *Limitation of libido*

3 *Limitation of growth of external genitalia*

Extragenital Effects

1 *Protein anabolic effect*

2 *Mineral retention effect*

3 *Inhibition of anterior pituitary.*

4 *Vasodilatory effect*

5 *General proliferation effect on epithelial tissue*

Effects with Other Hormones

Inhibition of gonadotropins.

Synergism with androgens in extragenital effects

Antagonism to androgens in genital effects

Effects of Excessive Oestrogens

Where oestrogens are present in elevated levels in the male, the normal effects of this substance may become exaggerated and produce undesirable results in a parallel manner to the effects of excessive androgens in the female, and the result is broadly classified as "feminisation", which might arise from causative factors such as

1. *Iatrogenic*—where the effects of exogenously administered oestrogens are reflected, or following castration, whereby normally circulating levels of oestrogens are no longer opposed by testicular androgens.

2. *Congenital hypogonadism*—such as the gonadal agenesis described by Klinefelter or other intersex states resulting in inadequate androgen output.

3. *Acquired testicular deficiency*—as at the climacteric.

4. *Excessive endogenous production*—arising from certain tumours of the testes or adrenal cortex.

5. *Liver dysfunction*—resulting in insufficient degradation and excretion of circulating oestrogens.

While the extragenital factors are concurrently involved, it is the genital effects which are predominant and these may be manifested as one or more of several forms. Impotence is common as is the development of secondary sex characteristics of the female type particularly in relation to fat distribution There may be proliferation of breast tissues giving rise to gynaecomastia and this is not infrequently accompanied by pigmentation of the nipple and areola. In severe cases regression of genitalia may occur.

The degree to which these alterations are produced is dependent on the age of the patient, on the severity and the duration of the causative stimulus but all that arise from excessive oestrogen levels are reversible and should disappear soon after the excessive production or administration has been reduced.

THE NORMAL REPRODUCTIVE CYCLE

This is the cycle of physiological events directed toward reproduction that culminates in a periodic shedding of the uterine mucosa when pregnancy is not achieved. The cycle may be regarded as consisting of three phases—(a) proliferative, (b) secretory, (c) decidual or desquamative—but desquamation is more generally included in the proliferative phase. Although these terms should apply specifically to a particular stage of endometrial development usage of "proliferative phase" and "secretory phase" has widened in scope to cover the various transformations produced by oestrogen in the first half of the cycle and progesterone in the second half. It must be remembered that the whole organism, as well as those organs directly concerned with reproduction, responds to the cyclical hormonal changes; disturbances of which not only cause abnormalities of menstruation and reproduction, but may be reflected in numerous other physiological functions

Cycle Length

The reproductive cycle is accepted for clinical purposes as commencing on the first day of menstruation and all events are dated in relation to this point The normal cycle length has long been accepted as 28 days but perfect regularity is extremely uncommon and the average woman will vary from her mean cycle length by 2 days in approximately one-third of her cycles. Clinically, 28 days plus or minus 3 is accepted as normal but studies have shown that only 53% of cycles may be expected to fall within this range.

Ovulation

In cycles of 28 days duration it has been shown that ovulation occurs most frequently on day 15 with variations ranging from day 12 to day 17 As with menstrual cycle length, on which it has a direct bearing, the time of ovulation varies and it has been shown to extend from day 7 to day 21

Phase Lengths

Since ovulation is a variable factor it follows that variations between the relative lengths of preovulatory and postovulatory phases are inevitable In 28-day cycles, the average length of each phase is 14 days but the range of variation is 7 to 21 days. In

cycles longer than 28 days the mean length of the preovulatory phase is more consistently increased than that of the postovulatory in which the range of mean values remains within 12 to 14 days and the overall range from 8 to 18 days.

Menstrual Duration and Blood Loss

Whereas the cycle length and phase length is distinctly variable in the individual woman, the duration of menstruation is reasonably constant for normal conditions. There is, however, a range of variation in groups of women and it is accepted that the average figure is 4·5 days with a normal range of 3 to 6 days Approximately 75% of normal women fall within this span.

Blood loss is also a variable factor and one that is difficult to assess accurately. A wide variation is encountered in menstrual loss but it is generally accepted that the average amount is approximately 30-40 ml. Since it is difficult to make a direct measurement and since information volunteered by the patient is always relative to previous menstrual history, care must be exercised in deciding what is normal for each individual when the amount of blood loss has a bearing on diagnosis.

THE PITUITARY-OVARIAN CYCLE

The elaboration of F.S.H. may be regarded as the initiating factor in the pituitary-ovarian cycle. The ovaries respond to F.S H. stimulus by ripening of Graafian follicles and the secretion of oestradiol which suppresses the F.S H. output and at the same time stimulates the production of L H. (see fig. 10). At approximately mid-cycle the level of L H. together with F.S H. is sufficient to bring about rupture of the Graafian follicle and ovulation. Under the influence of L.H. the corpus luteum is formed and secretion of progesterone and secondary levels of oestrogen is stimulated and continued production of increasing quantities of these steroids is maintained by L.T.H. The rising blood levels of oestrogen and progesterone eventually reach a point at which they suppress L H. and L.T.H. factors and as a result of reduced L.T.H. production the corpus luteum degenerates and there is a subsequent reduction of both progesterone and oestrogen production. The withdrawal of oestrogen and progesterone removes the inhibition that has been maintained on F S H. production and renewed secretion of this factor initiates the commencement of the next cycle.

As mentioned previously, this regular interplay is a self-regulating mechanism effected through the hypothalamus. The regularity of its normal function is therefore also subject to other influences directed at the hypothalamus (emotional, environmental, physiological). Consequently it is often suggested that the pituitary-ovarian mechanism is a delicately balanced relationship. It is obvious, however, from numerous clinical observations that pituitary-ovarian function is extremely flexible and resilient and capable of reasserting itself despite interference or even complete interruption of its activity. Examples of this may be seen under physiological circumstances (pregnancy) and under exogenous interference (induced pseudo-pregnancy—medical hypophysectomy etc).

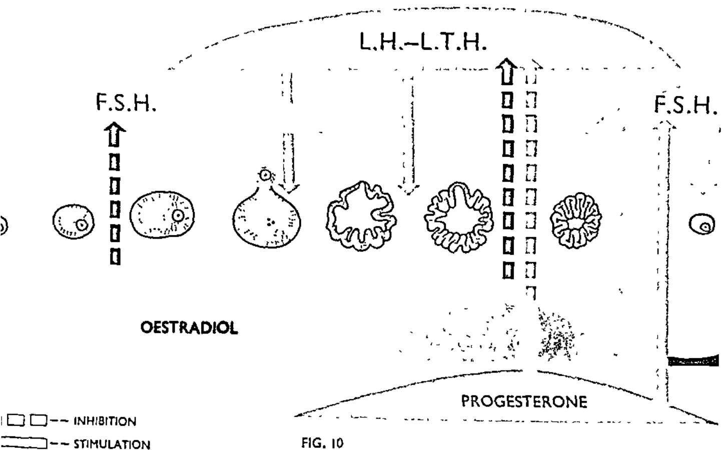

L.H.–L.T.H.
F.S.H.
F.S.H.
OESTRADIOL
PROGESTERONE
INHIBITION
STIMULATION

FIG. 10

The Uterine Cycle

The uterine body may be broadly subdivided into two sections (A) the myometrium which is constituted by two layers of muscle fibres separated by a vascular layer, (B) the endometrium which lines the uterine cavity and is differentiated into two major layers—a basal or regenerative layer and a functional or decidual layer.

Myometrial Cycle

During the preovulatory phase the muscle fibres lengthen and the myometrium adjacent to the basal endometrium becomes dense and toughened. In the later postovulatory phase this myometrium becomes soft and spongy and the uterine body becomes softer and larger in size. The spontaneous contractions of the uterus also present cyclical variations directly related to circulating hormones. During the proliferative phase contractions are frequent and of small amplitude whereas during the secretory phase the frequency diminishes and the amplitude increases.

Endometrial Cycle

Proliferative Phase—Under the influence of oestrogen the stroma of the endometrium proliferates from the basal layer, increasing to an eventual thickness of approximately 3 mm. Arteries penetrate into the stroma in a spiral fashion from the basal layer and there is a progressive development of glands which are regular in outline and which are inactive (non-secretory). These glands are further distinguished by the fact that the lumen occupies half the total cross-sectional diameter and the nuclei of the cells occupy a basal position.

Secretory Phase—Following the production of progesterone by the corpus luteum the oestrogen primed endometrium undergoes a transition designed to provide favourable conditions for nidation of the fertilised ovum and the sustenance of the ovum by provision of a high glycogen content and an extremely vascular bed. Under the influence of progesterone the glands take on a "saw toothed" or serrated appearance, become irregular and tortuous and the nuclei migrate toward the centre of the cells





















MENSES DAYS 1 to 5	PROLIFERATIVE PHASE DAYS 6 to 14	SECRETORY PHASE DAYS 15 to 28
CONSTRICTION	RE-EPITHELISATION	GLAND SERRATION
DILATATION	PROLIFERATION	GLYCOGEN PRODUCTION
NECROSIS	GLAND FORMATION	ARTERY CONVOLUTION
LYSIS	SPIRAL ARTERY FORMATION	ARTERY PENETRATION OF COMPACT ZONE
BLOOD POOLING	BASAL NUCLEAR POSITION	SUB NUCLEAR VACUOLISATION

FIG. 11

creating vacuoles (sub-nuclear vacuolisation). There is a secretory activity and glycogen is excreted via the lumen into the uterine cavity. The gland lumen becomes irregular and greatly increased in cross-section. The spiral arteries now become highly tortuous and convoluted and extend to the surface of the endometrium where a compact zone is now formed. This transformation reaches an optimal degree 6 to 8 days after ovulation, coinciding with the time when nidation might be expected. Towards the latter stages of the cycle a regressive type of change is induced. The glands become exhausted of glycogen and the nuclei revert to a basal position; the edges of the cells being broken and "feathered". There is leucocyte infiltration into the stroma of the endometrium which is now less compact and in which the cytoplasm of the cells is now visible. This exhaustive stage is referred to as a predecidual reaction.

Desquamative Phase—The effect by which gonadal hormones produce menstruation is known as "withdrawal effect". This phenomenon is shared by each of the gonadal hormones including testosterone and extends to their numerous derivatives. Under suitable conditions any of these substances will induce a menstrual-like shedding of the endometrium if their circulating level is raised sufficiently and then rapidly lowered through an adequate threshold. A sharp decline through a full threshold value would appear to be necessary for a clearly defined bleeding. When declining levels fail to clear this value prolonged "spotting" results.

Under normal physiological conditions menstruation is precipitated by a combined lowering of oestradiol and progesterone as the corpus luteum regresses. Since withdrawal of progestogens will duplicate this effect despite maintained oestrogen levels and since the converse does not apply, it may be assumed that progesterone withdrawal plays the principal role in initiating menstruation.

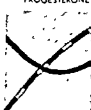
Menstruation

The endometrium, during the later stages of the cycle, undergoes shrinkage due to dehydration with the result that the tortuosity and coiling of the spiral arteries is intensified. With the rapid fall of hormone levels the arteries undergo constriction within the basal layer leading to a venous stasis. The resultant ischaemia

OESTROGEN



PROGESTERONE











1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28

7th DAY



14th DAY



21st DAY



28th DAY



MENSES DAYS 1 to 5	PROLIFERATIVE PHASE DAYS 6 to 14	SECRETORY PHASE DAYS 15 to 28
CONSTRICTION	*RE-EPITHELISATION*	*GLAND SERRATION*
DILATATION	PROLIFERATION	GLYCOGEN PRODUCTION
NECROSIS	GLAND FORMATION	ARTERY CONVOLUTION
LYSIS	*SPIRAL ARTERY FORMATION*	*ARTERY PENETRATION OF COMPACT ZONE*
BLOOD POOLING	BASAL NUCLEAR POSITION	SUB-NUCLEAR VACUOLISATION

FIG 11

properties of aborisation and Spinnbarkeit It is suggested by some workers that desquamation of the endocervical epithelium accompanies menstruation.

Vaginal Cycle

The vaginal mucosa consists of four layers—basal, outer basal, intermediate and superficial—and because of its site of origin reacts, as do other genital sites, to the cyclical variations of oestrogen and progesterone.

Proliferative Phase—Growth or proliferation of vaginal epithelium under the influence of oestrogens is of a distinct type showing, on vaginal smear, large flat single cells with small darkly staining (pyknotic) nuclei Under the optimal influence of oestrogen the cells of this cornified squamous epithelium are separated and appear on a clear background and since they are predominantly eosinophilic the prepared vaginal smear takes up acid dyes and stains red. The vaginal epithelium at this stage is rich in glycogen which encourages growth of Doderlein bacilli and these convert the glycogen to lactic acid. The high concentration of this acid is responsible for the preovulatory acid medium (pH = 4 to 4 5)

Secretory Phase—Under the influence of progesterone the microscopic picture of the vaginal smear also undergoes rapid changes The cells become clumped together in groups, their edges are folded and crumpled and the degree of pyknosis is lost as the cells develop larger elongated nuclei Immediately postovulatory there is a marked preponderance of acidophils and the clumps of these intensely red staining cells are referred to as "rosettes". Subsequently there is an increase in basophils with a corresponding up-take of basic dyes to give blue staining Glycogen content in the vaginal secretions drops so that Doderlein bacilli activity and resultant lactic acid production fall, giving a pH of 6 5 to 7.

Fallopian Tube Cycle

The epithelial lining of the fallopian tubes is comprised principally of ciliated and non-ciliated columnar epithelium, which exhibit a cyclical response as does the general motility of the tube itself

leads to early stages of necrosis throughout the endometrial tissues and possibly initiates the effect of lytic enzymes. Periodic vasodilation *permits an onrush of blood into the weakened* tissues and bleeding through diapedesis, rupture of arterioles and destruction of venous return ensues. Preliminary bleeding through the surface of the endometrium is followed by decimation of the stroma and separation from the basal layer by the formation of blood pools Enzymatic action breaks down the stromal tissues, destroys clotted blood and the blood fibrinogen and prothrombin and the menstrual products are discharged as a serum and mucus mixture. Myometrial contractions aid the evacuation of the menstrual flow and also assist in haemostasis. With the reappearance of oestrogen, epithelialisation and reproliferation bring menstruation to completion.

The normal duration of menstruation is 3 6 days and the average blood loss is 30-40 ml It is generally accepted that for average hygiene 15 sanitary pads represent a normal menstrual loss and this measure provides a convenient basis for comparison.

Cervical Cycle

The cervix is constituted mainly by connective tissue together with some muscle fibres and contains numerous racemose glands While its epithelium has the same origin as the epithelium of the uterus and upper two-thirds of the vagina, the tissue structure is not constant throughout, being identical in appearance and cyclical activity with the vagina on the vaginal aspects of the cervix up to the external os The internal aspect (endocervix) is of a ciliated columnar type and the mucosal stroma and the glands follow a cyclical pattern more akin to that of the endometrium

Proliferative Phase—Under the influence of oestrogen the mucosa of the endocervix tends to undergo a transformation to stratified squamous epithelium and the glands become highly active The secretions of the glands become copious, thin, highly alkaline (pH = 8-9) and are rich in protein and carbohydrate When dried on a clean slide *the mucus crystallises in a typical "fern-leaf"* pattern (aborisation) and also develops a tensile strength that permits it to be stretched into threads (Spinnbarkeit)

Secretory Phase—Under the influence of progesterone the cervical mucus becomes viscid, scanty and less alkaline It also loses the

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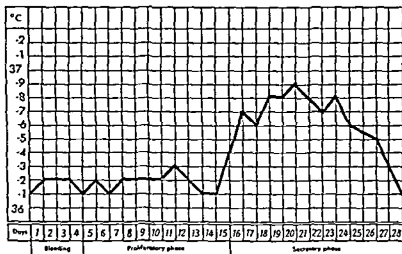
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CYCLICAL CHANGES IN OTHER SITES

As pointed out previously, the effects of sex hormones are reflected throughout the whole organism in extragenital as well as genital functions Systemic changes in functions and sites not directly allied with reproduction are not uncommon and in some cases are sufficiently well defined as to reflect specific endocrine activity and often have an application in clinical practice.

Thermogenic Cycle

The basal body temperature is directly influenced by circulating progestogens. With the occurrence of ovulation there is a slight drop in temperature and with the advent of significant progesterone levels there is a sudden elevation (thermal shift) in temperature averaging 0 8 to 1·0 degrees F. achieved over 2 to 3 days. This level is maintained throughout the period of corpus luteum activity and declines rapidly after luteal regression just prior to menstruation. A cycle exhibiting such a "shift" is classi-



NORMAL BASAL TEMPERATURE

FIG 12

Proliferative Phase—Under the influence of oestrogen there is a uniform growth of the columnar cells and the peristaltic contractions are progressively increased in amplitude and frequency. This rate increases from approximately 4 per minute to a peak of approximately 10 per minute immediately after ovulation and this peak motility is accompanied by maximum amplitude.

Secretory Phase—Under the influence of progesterone there is a regression of the ciliated columnar while the non-ciliated cells display secretory activity and project above the ciliated forms to give an uneven surface There are also alterations in nuclei position and frequency and amplitude of contractions gradually wane.

Breast Cycle

Although in certain women cyclical variations in breast size and in breast tissues can be observed clinically during the later half of the secretory phase (see p 39), cyclical changes related to each phase are not so clearly defined. There would, however, appear to be a phase of proliferation and regression involving the ducts.

General Systemic Variations

Although they may not be as pronounced as some genital variations during the cycle it is reasonable to assume that cyclical variations associated with any of the extragenital effects may occur. This is more distinctly illustrated in cyclical sodium and water retention and other somatic and psychic effects encountered in the premenstrual syndrome (see p. 102).

fied as a "biphasic", although this term is extended to cover cycles exhibiting other criteria of postovulatory changes. Where pregnancy occurs, the temperature remains elevated over the first 100 days of pregnancy.

Blood Chemistry Cycle

It is generally accepted that a cyclical variation exists in certain blood components Menstrual blood loss would appear to be relatively heavy in iron and it has been established that an average of approximately 20 mg. (range 4 to 65 mg.) is lost with each menstruation. Red cells and leucocytes are elevated during the late secretory phase and fall during menstruation whereas eosinophils are decreased during the secretory phase It has, in fact, been suggested that the occurrence of ovulation can be confirmed by leucocyte count.

Vascular Cycle

Some evidence exists to support the contention that vascular changes, parallel with other cyclical changes, do occur. These changes would appear to involve peripheral vessels and oestrogen tends to produce a vasodilatory effect whereas progesterone induces capillary fragility and vascular spasm This is most apparent in the bulbar conjunctiva and is possibly related to the phenomenon of conjunctival haemorrhage during menstruation ("menstrual red-eye")

Skin Changes

Apart from cyclical variations of peripheral vessels and water retention which may affect the skin there is evidence which suggests a cyclical variation in skin pigmentation in some women These changes of pigmentation are most common in the peri ocular and nipple areola skin and would appear to be due to premenstrually increased sensitivity to ultra violet light Cyclical variations in melanophore expanding hormone rather than gonadal hormones would account for this phenomenon but pigmentation of the nipples is associated with oestrogens at puberty and during exogenous administration

(a) The genital effects of oestrogen are reflected in rapid growth of all the genitalia together with proliferation of the endometrium. Irrespective of whether or not ovulation occurs, rising levels of oestrogen will eventually suppress the pituitary activity with the result that follicular production will fall and the proliferated endometrium will shed in the first menstrual bleeding known as the menarche. It is unlikely that ovulation will be achieved in this or subsequent early cycles and it is therefore natural for bleeding to occur at irregular and usually prolonged intervals and also that relative infertility will exist. It is also likely that during this phase of adjustment, temporary disruption of the pituitary-ovarian interplay might occur. An example of such variation is seen in the tendency for follicles to persist giving rise to a marked menstrual disorder known as metropathia haemorrhagica (see p. 96). With the achievement of regular ovulation, a normal cyclical pattern will become established, providing a well-defined cycle which is usually achieved by the 18th year but may take longer in individual cases.

(b) The extragenital effects of oestrogens are reflected principally in the development of secondary sex characteristics as described on p. 37 and these obvious physical changes, to an extent, precede the menarche and usually provide a physical indication of forthcoming menstruation

(c) The initial hypothalamic activity is not selective and until stabilisation is achieved, the pituitary hyperactivity during puberty is not confined to gonadotropins. As a result of the release of other tropic factors, associated physical changes are apparent Increased growth hormone promotes rapid growth of the long bones but the continuation of this effect is subsequently diminished by oestrogen induced closure of the epiphyses. General metabolism may be varied by increased stimulus to the thyroid by thyrotropic hormone and increased output of A C T H will stimulate the production of adrenal steroids In creased adrenal activity is directly reflected by obvious androgenic effects, such as the increased sebaceous gland activity which gives rise to the acne commonly encountered at this stage The effect of adrenal androgens is also observed in the growth of pubic hair (adrenarche) and the growth of axillary hair Hypothalamic hyperactivity is also reflected in the reflex disturbances of the centre of psyche and the autonomic nervous centre Wide

PHASES OF ENDOCRINE ACTIVITY

The endocrine activity throughout the life of the female may be divided into 3 well-defined phases: (A) quiescence, (B) maturity and (C) senescence. The transition from one phase to the next occupies a relatively short period during which marked changes in both endocrine and other physiological functions take place. These transitional periods are known as the "menarche" and the "menopause".

Quiescence

During intrauterine life the foetus is exposed to the effects of circulating maternal steroids and this is reflected in the genitalia at birth. The endometrium is proliferated and parallel proliferation of the vaginal mucosa which is quite marked, can be observed. Proliferation may also be observed in the breasts of both male and female neonates to the extent that some excretion from the nipples can occur. However, the influence of the maternal hormones soon declines, producing a regression in the previously stimulated sites and in the case of the uterus this decline in steroid levels may precipitate a small withdrawal bleeding With the exception of endocrine disturbances leading to sexual precocity, there is very little endocrine activity until the onset of puberty

Maturity

At the onset of puberty there is a very rapid and marked transformation in the female. This is precipitated by a sudden pituitary activity and is initiated *principally* by the secretion of relatively high levels of gonadotropins The mechanism behind the sudden onset of this pituitary hyperactivity is not understood but presumably is initiated through increased hypothalamic activity The resultant transition from girlhood to sexual maturity is naturally dependent on a normal response by the ovaries to the pituitary stimulus

The ovaries should respond to the gonadotropins by an increase in size and weight, the development of Graafian follicles and the secretion of *follicular hormone* The various effects, which are achieved at this time, may be classified in 3 groups (a) those arising from the genital effects of oestrogens, (b) those arising from the extragenital effects of oestrogens and (c) those arising from pituitary and hypothalamic influence on other sites

(a) The genital effects of oestrogen are reflected in rapid growth of all the genitalia together with proliferation of the endometrium. Irrespective of whether or not ovulation occurs, rising levels of oestrogen will eventually suppress the pituitary activity with the result that follicular production will fall and the proliferated endometrium will shed in the first menstrual bleeding known as the menarche. It is unlikely that ovulation will be *achieved in this or subsequent early cycles* and it is therefore natural for bleeding to occur at irregular and usually prolonged intervals and also that relative infertility will exist. It is also likely that during this phase of adjustment, temporary disruption of the pituitary-ovarian interplay might occur. An example of such variation is seen in the tendency for follicles to persist giving rise to a marked menstrual disorder known as metropathia haemorrhagica (see p 96). With the achievement of regular ovulation, a normal cyclical pattern will become established, providing a well-defined cycle which is usually achieved by the 18th year but may take longer in individual cases.

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mood variations and changes of behavioural pattern are to be expected in conjunction with vasomotor disturbances (flushing-tachycardia-fainting etc.) during the transitional period.

Once established, a normal menstrual pattern should be maintained throughout the remainder of the sexually mature span. The cycle, of course, is subject to interruption by such factors as pregnancy and also the functional, pathological and other influences as set out in the section dealing with menstrual cycle disturbances.

Senescence

The end of reproductive activity and the commencement of gonadal senescence is known as menopause. As at puberty, the mechanism underlying the loss of ovarian functions is not clearly understood. Regular ovulation which is the last event achieved in the establishment of the cycle, is the first thing lost and variations in the menstrual cycle, as observed at a similar stage during puberty, are likely to occur as a consequence. As a patient advances into menopause the ovaries undergo further involution and cease all response to gonadotropin stimulus. The consequent loss of oestrogen secretion leads to loss of genital effects which is reflected principally in the loss of menstruation. Of the extragenital effects, the loss of pituitary inhibition is the most marked and results in a hypothalamic and pituitary hyperactivity which gives rise to marked reflex disturbances of psyche and the central nervous system parallel to, but more intense than, those seen at puberty. The continued loss of both genital and extragenital effects may eventually become apparent in a number of atrophic and regressive changes

CLINICAL EVALUATION OF ENDOCRINE ACTIVITY

In the treatment of problems associated with the menstrual cycle care must be taken to rule out all systemic and pathological conditions as causative factors. When the problem is considered to be an endocrine disturbance, various methods are available by which the hormonal activity in the menstrual cycle may be determined

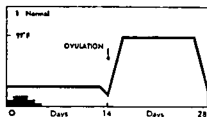
1. **Basal Body Temperature Graph**
2. **Endometrial Biopsy**
3. **Vaginal Smear**
4. **Cervical Mucus Tests**
5. **Endocrine Assays**

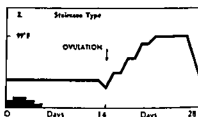
Basal Body Temperature Graph

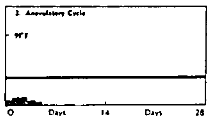
This is a simple and informative procedure based on the temperature increasing effect of progesterone. The basal body temperature is taken on awakening, before rising, drinking or smoking The serial morning temperatures are plotted on large-scale graph-paper and it is preferable that the temperature should be taken rectally Under normal conditions the temperature remains at a fairly constant level until the time of ovulation when, after a slight drop, it rises by approximately 0·8° F. and remains elevated from 9 to 13 days without much variation From the height, shape and length of the graphed thermal increase the occurrence of ovulation can be established and a qualitative assessment made of progesterone activity in the cycle (see fig 13)

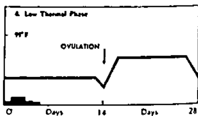
Endometrial Biopsy

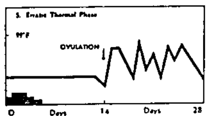
A small piece of endometrium, when removed surgically, stained and examined under the microscope, will show typical signs of oestrogen and/or progesterone activity as described on p 51 The biopsy, where possible, should be carried out 3 days prior to menstruation and as well as a general histological examination, an estimate is made as to the day in the cycle to which this tissue has developed By comparing the date of the endometrium,


1 Normal
99°F
OVULATION
O
Days
14
Days
28


2. Staircase Type
99°F
OVULATION
O
Days
14
Days
28


3. Anovulatory Cycle
99°F
O
Days
14
Days
28


4. Low Thermal Phase
99°F
OVULATION
O
Days
14
Days
28


5. Erratic Thermal Phase
99°F
OVULATION
O
Days
14
Days
28

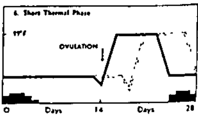

6. Short Thermal Phase
99°F
OVULATION
O
Days
14
Days
28

FIG. 13

as established by the pathologist, with the known date of the biopsy, as checked against the actual date of menstruation, endocrine activity may be assessed The occurrence or otherwise of ovulation may be confirmed, precise knowledge of endometrial development obtained and since this reflects hormonal influence, a qualitative assessment of ovarian activity can be established.

Vaginal Smear

A thin scraping from the vaginal mucosa is taken, prepared, stained and examined under the microscope. Under oestrogen influence the vaginal epithelium proliferates and the histological picture of the cells in the smear should be that of a red-staining, cornified, squamous epithelium, rich in glycogen, with the cells showing small "pyknotic" nuclei. During the secretory phase of the menstrual cycle this tissue regresses and the cells should be clumped together, crumpled around the edges with larger nuclei which stain weakly. The tissue now stains blue and glycogen is no longer demonstrated. As the vaginal epithelium responds to follicular hormone and progesterone by typical changes, in the same manner as does the endometrium, it reflects precisely the phases of the endometrium. Therefore if the histological picture in the vaginal epithelium is atypical for that part of the menstrual cycle on which the smear is taken, the endometrium should also show an atypical development.

From the vaginal smear it is possible to confirm the absence or otherwise of ovulation and to obtain a qualitative assessment of hormonal levels. The vaginal epithelium would appear to be a particularly sensitive register of oestrogenic stimulus and this fact is utilised in a technique for oestrogen assay (see p 68)

Cervical Mucus Tests

The cervical mucus secretion responds remarkably to oestrogen and progestogen activity Under the influence of oestrogen the secretions are thin and copious, showing properties of cohesion which allow the mucus to be stretched into strings. The mucus is alkaline, rich in protein, carbohydrate and saline and when dried on a slide will crystallise out in the shape of ferns Progesterone brings about a marked diminution of secretion, the mucus becomes viscid, acidic and scanty and loses the above properties

"Thread Test"—Normal cervical mucus prior to and at the time of ovulation, is capable of being stretched out into a thread of at least three inches long before it breaks. This property is often described as "Spinnbarkeit" and is a "rough-and ready" test for normal mucus but not as reliable as the fern test.

"Fern Test"—When normal cervical mucus, obtained just prior *to and at the time of ovulation, is spread on a glass slide* and allowed to dry, *it crystallises out in the shape of ferns or palm* leaves (arborisation) *Other body mucus does the same thing but* it is only in the cervix that this phenomenon is under the control of oestrogens. In obtaining the mucus it is important not to use any apparatus that is wet with saline, as the crystal formation is dependent largely on this electrolyte. If a typical pattern is present, then the cervical mucus may be regarded as normal for this phase of the cycle. Neither of the mucus tests is particularly *sensitive and the only definite information which they provide* relates to the occurrence or otherwise of ovulation.

Endocrine Assays

Progesterone

The levels of progesterone circulating in the blood may be assessed by the Hooker-Forbes assay which is based on the degree of hypertrophy which this substance produces in stromal cell nuclei in the endometria of ovariectomised mice. Accurate evaluation may also be made chemically by the use of chromatography but for all clinical purposes the measurement of metabolites in the urine is usually adopted. The excretory metabolites of progesterone may be classified in 3 principal groups.

(a) pregnanediones, (b) pregnanolones, and (c) pregnanediols

Of the numerous progesterone metabolites, pregnanediol is the product usually selected for assay by chromatographic methods While only 20% of progesterone production is excreted in this form the establishment of norms provides a comparative basis by which pregnanediol levels can be used to evaluate the activity of the corpus luteum, or the placenta. The average excretion figures (see fig 14) are 1 12 mg /24 hours during the proliferative phase and 3 3 mg /24 hours during the secretory phase. A two- to three-fold rise of pregnanediol excretion may be accepted as conclusive proof that ovulation has occurred and since these

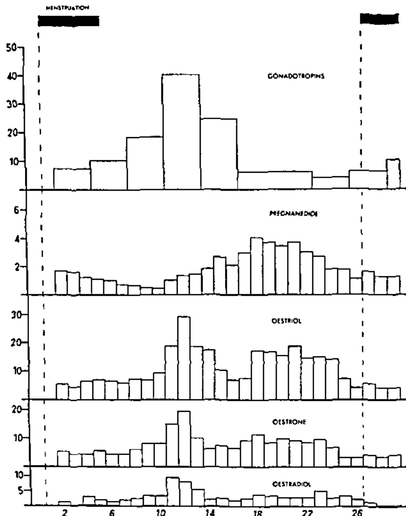


FIG 14

DAILY EXCRETION RATES

GONADOTROPINS—Measured in Human Menopausal Gonadotropin (H M G) units per twenty-four hour urine as assessed by mouse uterus and hypophysectomised rat prostate tests

PREGNANEDIOL—Measured in milligrams per twenty four hour urine

OESTRIOL
OESTRONE
OESTRADIOL } —Measured in micrograms per twenty four hour urine

After Brown, Klopper and Loraine *J of Endocr* 17 101, 1958
Reproduced in part by kind permission of J A Loraine

measurements are conducted serially, a close estimation of the date of ovulation can be made.

Oestrogen

Accurate measures for the estimation of blood levels of oestradiol have recently been developed but are too tedious for routine use. Consequently current assay techniques are directed at the measurement of excreted urinary oestradiol and its major metabolites. Bio-assay techniques are based on vaginal cornification (Allen and Doisy test) or increase in uterine weight in castrated immature rats Chemical methods employ either colorimetric or fluorimetric techniques. The average excretion of the major metabolite, oestriol, at day 1 of the cycle is 6 μg/24 hours. This rises to an approximate mid-cycle peak of 27 μg/24 hours and after a temporary fall in excretion, recovers to a luteal phase peak of 22 μg/24 hours (see p. 67). Although urine is the main excretion pathway of oestrogens, the excretory products (as with pregnanediol) do not reflect total production but once again, established norms provide a basis for accurate comparisons Oestrogen assays therefore provide an accurate quantitative register of oestrogen production from the Graafian follicle, corpus luteum and also placenta and since it is now accepted that demonstration of a "preovulatory peak" is indicative of ovulation, such serial assays may be used to determine the occurrence or otherwise of ovulation.

Androgens

Assays of androgens in the blood or urine are possible by bio assay techniques such as the restoration of capons' combs or weight increase in chicken combs (chick comb test). However, assays of blood levels by these methods are not particularly satisfactory and precise chemical methods recently developed for plasma levels of testosterone are not, as yet, suitable for clinical application. It is therefore more usual to assay the numerous excretory products of testosterone and other secreted steroids which are grouped as 17-ketosteroids. More than eight of these can be separated and measured by chromatography but in practice the results are usually expressed in terms of total unfractionated 17-ketosteroids The average excretion in females is 7 mg/24 hours but this may vary according to age

Gonadotropins

In the assay of gonadotropins, whether pituitary or chorionic in origin, chemical methods are not as yet particularly efficient and bio-assay techniques are therefore relied upon. In normal clinical practice no attempt is made to separate the pituitary factors and the combined urinary output is measured. The assays are based on measurement of the increase in weight of various genitalia (uterine weight test, ventral prostate weight test etc.) in experimental animals (rats and mice principally) and for reliable results it is preferable that the animal be hypophysectomised. Results achieved with the test material are compared with those achieved on a standard substance (H M G 20) and are expressed in terms of human menopausal gonadotropins (H.M.G.). The range in mature females is 3 to 34 H.M.G. units/24 hours with a mean of 10 H.M.G./24 hours. Chorionic gonadotropin is usually assayed on a qualitative basis by means of response induced in experimental animals

1. Ascheim-Zondek reaction—where injection of suitably prepared urine results in the production of haemorrhagic follicles and corpora lutea in the ovaries of immature mice if sufficient H C G. is present (positive reaction).

2. Friedman Test—where similar results are produced in the ovaries of rabbits.

3. Kupperman Test—also known as the "rapid rat test" in which hyperaemia of the ovaries represents a positive response

Of lesser reliability but more commonly used as a means of pregnancy diagnosis are:

1. Hogben reaction in which injection of suitably prepared urine into female frogs of the Xenopus strain results in extrusion of ovum as a positive result

2 Galli-Mainini reaction in which a positive response is indicated by the expulsion of sperm in a wide series of male frogs

A more recent development which provides an extremely sensi- [illegible]

haemagglutination technique in which measurement is assessed from a typical agglutination inhibition pattern

MECHANISM OF CONCEPTION AND PREGNANCY

The mechanism by which fertilisation, conception and successful pregnancy is promoted has already been described in detail (albeit as separate effects) in those sections dealing with the action of pituitary and gonadal hormones. It is important to remember that the sole purpose of these numerous effects is the establishment and maintenance of a normal, full-term pregnancy. When sperm are deposited in the vagina at the time of ovulation, the proliferative effects of oestrogen in both the endometrium and the vaginal mucosa are at their optimal height. The vagina now presents a highly acid medium (pH 4) which is extremely antagonistic to sperm that are accustomed to and require a more alkaline medium approximating that of seminal fluid (pH 7 to 8). It is now accepted that exposure to the optimally acid vaginal medium will deprive sperm of fertilising power within a matter of minutes and destroy them within 2 to 3 hours. However, the same oestrogenic effect provides a copious flow of more alkaline mucus discharged from the cervical os down the hostile wall of the vagina and under the direction of chemotaxis the sperm rapidly migrate towards the point of highest alkalinity, namely the endocervix (pH 8 to 9). From this point they traverse the uterine cavity and the fallopian tubes with remarkable rapidity.

With the occurrence of ovulation the ovum with its surrounding "corona radiata" of granulosa cells is swept into the abdominal cavity and by some unknown means finds its way into the infundibulum of the fallopian tube which under the influence of oestrogen is now in an optimal stage of proliferation and presents maximum frequency of peristaltic contractions. The ovum is now propelled by the waves of peristalsis along the fallopian tube towards the uterus

Fertilisation

Although fertilisation of the ovum can occur wherever it encounters sperm, this event is usually accomplished in the distal end of the fallopian tube, and due to the relatively short fertile life of ovum (12 to 24 hours) and sperm (24 to 48 hours) fertilisation is confined to a relatively short time interval. Once again the precise mechanism of this event has not been clarified but it

is known that all sperm carry a substance capable of breaking down intercellular cement (hyaluronidase) and recent investigations would suggest than an "antigen-antibody" reaction is responsible for the fact that only one sperm usually penetrates the ovum· This antigen theory which has been demonstrated *in vitro* and confirmed in some lower species is based on the fact that the surface of the vitelline capsule of the ovum carries a receptor substance ("fertilisin') which reacts with a corresponding substance of the sperm head ("anti-fertilisin") to cause agglutination of sperm The vitelline membrane is perforated and the underlying plasma membrane projects through these perforations When the first sperm has achieved penetration, the plasma membrane retracts so that subsequent sperm contact the vitelline membrane only and consequently react by agglutinating After penetration, the sperm fuses with the nuclei of the ovum and there is rapid mitotic division to form the first stage of development (morula) By the time the morula reaches the uterine cavity, an antrum has formed within the cells, giving rise to the blastocyst stage

Nidation

The zygote arrives in the uterus some 3 to 5 days after ovulation and floats freely in the uterine cavity for a further 24 to 48 hours during which time further development has led to the production of a cystic stage in which the antrum, containing the amniotic cavity and the yolk sac, is surrounded by mesodermal tissues known as the chorion From the chorion numerous fingerlike processes develop (chorionic villi) to form the trophoblast and at this stage of development the zygote is classified as a blastocyst In the interval that elapses between the occurrence of ovulation and the development to this stage (approximately 7 days), the corpus luteum is active and has reached optimal levels of progesterone secretion. The secretory transformation that occurs in the endometrium provides glycogen for the sustenance of the zygote while it is floating freely in the uterine cavity and ensures the maximum development of a highly vascular uterine bed By a process of erosion, the chorionic villi attach the blastocyst to the endometrium and this union is classified as nidation Interference with progesterone production that results in inadequate transformation of the endometrium and secretion of glycogen before nidation, will result in death of the developing zygote

MECHANISM OF CONCEPTION AND PREGNANCY

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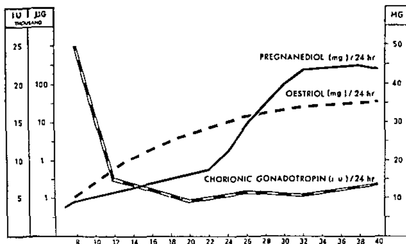


FIG 15

PREGNANCY EXCRETION RATES

At full term the average amounts excreted per twenty-four hours are approximately as follows

Oestrone	2 00 mg
16–*epi*oestriol	0·75 mg
16α–hydroxyoestrone	2 00 mg
Oestradiol–17β	0·75 mg
Oestriol	30·00 mg
Pregnanediol	40·00 mg

Peak production of H C G. during the first trimester may vary, in different-subjects, from 20,000 to 100,000 i u per twenty-four hour urine or per litre of blood serum

After J Loraine *Clinical Application of Hormone Assay* and R Shearman *J. Obst and Gyn* LXVI, No 1, 1959—reproduced by kind permission of the authors

Pregnancy

Pregnancy may be regarded as established from the time of nidation, but as it has been previously shown, continued production of progesterone and of oestrogen is required for continuation of pregnancy. Should hormone levels fall at this stage, the endometrium will respond in the usual way by desquamating and pregnancy will be terminated. The natural regression of the corpus luteum is prevented by a gonadotropin which is secreted by the chorionic villi. This substance (human chorionic gonadotropin—H.C.G.) is strongly luteinising in its effect and stimulates the corpus luteum to increase in size and production. H.C.G. appears in the urine in small amounts after nidation (i.e. approximately 7 days after ovulation) and increases to significant levels by the 14th to 16th day, but it is not until the 6th or 8th week of pregnancy that the level is sufficiently high to enable accurate bio-assays. The increased output of progesterone from the corpus luteum of pregnancy intensifies the secretory transformation in the cervical mucus and the endometrium. A mucus plug is formed in the cervical canal and the endometrium surrounding the villi undergoes an intense transformation (decidual reaction) which leads to the formation of the maternal half of the placenta. The rest of the endometrium undergoes a similar temporary transformation but tends to regress during the latter stages of gestation. The villi continue development and form the foetal half of the placenta which is usually fully functional by the 12th to 14th week of pregnancy. As well as providing the site of nutrition and excretion for the foetus the placenta is also a completely independent endocrine gland which produces increasingly large quantities of both oestradiol and progesterone and by the 12th to 14th week this organ assumes full production of these hormones and as chorionic gonadotropin production declines, the corpus luteum regresses The increase of oestrogen and progesterone (see fig. 15) provides for rapid growth of the uterus to accommodate the developing foetus, sedates the uterine musculature, inhibits pituitary activity so that the normal pituitary-ovarian cycle is suppressed throughout pregnancy and prepares the breasts for lactation As at nidation, interference with progesterone output during the first trimester is likely to cause termination of the pregnancy

count or by sperm penetration of cervical mucus (e g, Sim's Test)

5 *Cervical Factor*—The cervix must be normal and the cervical mucus at the time of ovulation must satisfy the "thread test" and "fern test"

6. *Tubal Patency*—This must be proved by Rubin's Test (CO_2 under pressure) or X-ray with opaque media (hystero-salpingography)

7. *Endometrial Biopsy*—The biopsy, taken three days prior to menstruation, is to ensure that there is an adequate secretory phase for successful nidation The loss, in menstruation, of a poorly nidated ovum is strictly speaking an abortion, but presents clinically as infertility

Application of Hormone Therapy in Infertility

Uterine Hypoplasia

Hypoplasia of the uterus need not necessarily constitute a cause of infertility but where all other possibilities have been eliminated, the presence of an underdeveloped uterus would warrant treatment Stimulation of uterine growth may be attempted by three forms of therapy

1. *Cyclical Oestrogen Therapy*

Dosage Primogyn-Depot (oestradiol valerianate): 10 mg i m on the 5th day of each cycle until development is satisfactory Response to this type of therapy may not be particularly satisfactory and either of the following alternatives may be preferred

2. *"Pseudo-Pregnancy" Therapy*

This is undertaken with high doses of an oestrogen and a progestogen to imitate the hormonal situation of early pregnancy During the pseudo pregnancy therapy the uterus is softened and enlarged, resembling by the end of treatment the changes of early pregnancy These changes regress slightly when treatment is stopped but in the majority of cases a definitive growth, equal to 2 to 3 cm. in the uterine sound length, persists The course covers 8 weeks and the dosages used will cause the patient to be amenorrhoic during treatment but on withdrawal of the therapy a heavy "withdrawal bleeding" occurs and a decidua is sometimes shed After 4 to 6 weeks regular cycles resume and these

HORMONE THERAPY IN DISTURBANCES OF FERTILITY AND PREGNANCY

STERILITY AND INFERTILITY IN THE FEMALE

Sterility is usually defined as an inability to conceive. Clinically, however, a marriage is regarded as infertile if, after two years, pregnancy has not been accomplished, irrespective of whether or not there have been previous pregnancies. The percentage of sterility on this basis is high (1 in 6 = 16 per cent).

Before the necessity for any hormonal therapy can be evaluated an attempt must be made to exclude systemic disease, pelvic pathology and other non endocrine factors which may be playing a part in the production of infertility. The sequence for examination and elimination of sterility factors is usually as follows:

1. *General History and Physical Examination*—The patient should have a thorough overhaul, special attention being paid to the exclusion of chronic disease such as tuberculosis, diabetes or chronic nephritis Hormonal abnormalities such as thyroid or adrenal disease may be of the utmost importance and hirsutism, even though mild, warrants 17-ketosteroid investigation. An evaluation must be made of any emotional disorders. Advice on rest, diet and timing of coitus is given, whilst mild sedation during the second half of the cycle may be instituted and continued throughout the duration of the various tests

2. *Pelvic Pathology*—This must be eliminated as a possible factor and may be either congenital, i e. bicornuate uterus, gross under development, etc., or acquired, i e fibroids, endometriosis, cervicitis, etc.

3 *Anovulatory Cycles*—Ovulation must be proved, preferably by basal body temperature graph The patient is encouraged to continue graphing temperatures throughout the entire course of examinations and treatment in order to disclose possible corpus luteum deficiency, optimal time for conception, correct timing for correction of unfavourable cervical mucus and the earliest diagnosis of pregnancy

4 *Male Sperm Count*—Once the preceding steps have been carried out and the patient appears normal, examination of the male for sperm deficiencies must be completed either by sperm

inducing a rhythmic pituitary stimulus via the feedback mechanism (for dosage see substitution therapy, p 85)

(b) Rebound Therapy—There is evidence that when the pituitary is suppressed and subsequently released there is rebound response leading to higher activity with resultant increased gonadotropin output. Such suppression may be attempted by either of 2 methods:

1 "Pseudo-pregnancy" therapy—In the same manner as applied to uterine hypoplasia (see p 76)

2. Cyclical rebound therapy (after Rock *et al.**)—where inhibition and release of pituitary activity is conducted in a cyclical fashion.

Dosage Primolut-N (nor-ethisterone): 5 mg. tablets t d s. from the 5th to 25th day of the cycle for 3 or 4 cycles.

Alternative Dosage Anovlar (nor-ethisterone acetate + ethinyl oestradiol): 1 dragee daily from the 5th to 25th day of the cycle repeated for 3 or 4 cycles.

Unfavourable Cervical Mucus

In order to ensure that the cervical mucus will be suitable for sperm penetration small amounts of oestrogen may be given prior to ovulation.

Dosage Progynon B Oleosum (oestradiol benzoate) 5 to 10 mg i m. 1 to 2 days prior to ovulation as shown by the basal body temperature graph

Corpus Luteum Insufficiency

Since this may result in faulty nidation, progesterone is administered to ensure adequate secretory transformation for proper nidation of the ovum

Dosage Primolut-N (nor-ethisterone): 5 to 10 mg daily from the 18th to 25th days of the cycle or

Proluton-Depot (hydroxy-progesterone-capronate) 125 mg. i.m. on the 18th day of the cycle.

Idiopathic Infertility

When there is no apparent cause for sterility, cyclical rebound therapy may be employed. The application of this therapy is

* Rock *et al. Rec Prog Hormone Research* 13 323 (1957)

may apply even in cases where irregular ovarian function has previously existed.

Dosage Primogyn-Depot (oestradiol valerianate): 10 mg i.m. *weekly for 4 weeks then increasing to 20 mg. weekly for the remaining 4 weeks plus*

Proluton-Depot (hydroxy-progesterone-capronate): 125 mg i.m *weekly for the first 2 weeks, increasing to 250 mg weekly for the* second 2 weeks, increasing to 375 mg. weekly for the third 2 weeks, increasing to 500 mg. weekly for the final 2 weeks of *therapy*

3. *Direct Injection*

The cyclical injection of a long-acting oestrogen directly into the substance of the cervix may produce striking uterine growth within a short space of time.

Dosage Primogyn-Depot: *10 mg into the cervical substance* weekly for 3 to 4 weeks.

Failure of Ovulation

There is no certain way of stimulating ovulation and the prognosis is poor in the majority of anovulatory women. The outlook is more hopeful in patients with adrenal hyperplasia (treatment by suppressive corticoid steroids such as prednisolone) or the Stein-Leventhal syndrome (treatment by bilateral wedge resection of the ovaries). In some patients the cause is psychological *and psychotherapy may sometimes succeed. Where no clear aeti*ology exists, hormone therapy is frequently tried and may take the form of direct stimulation of the ovaries or attempts to stimulate the pituitary into greater output of gonadotropins

Gonadal Stimulation—Recent advances in the extraction of relatively pure forms of human F S H. have led to reasonable success in the production of ovulation in anovulatory women. However, the availability of this substance is so limited that it is restricted to research rather than clinical applications Stimulation of the ovaries can be attempted with gonadotropins that are available but reliable results should not be expected (for dosage see primary amenorrhoea, p. 83)

Pituitary Stimulation—Attempts to increase gonadotropin output may be undertaken in two forms.

(a) Cyclical oestrogen and progestogen administration aimed at

estimations are not always practical and examination of the os not always desirable, there is no harm in using progesterone empirically and the chances of success, in the true threatened abortion, when using suitable progestogens in high dosages, are good Treatment must be early and adequate.

Dosage Proluton-Depot (hydroxy-progesterone-capronate): 500-750 mg. i m

For further treatment in those cases which settle down Proluton-Depot 250-500 mg. i m. should be given weekly during the first half of pregnancy.

Habitual *Abortion*

The role of hormonal therapy in recurrent abortion has been the subject of much controversy since various workers have claimed that statistically there is little to choose between any therapy, be it hormonal, bed rest, sedation or even psychotherapy. More recent evaluations of this subject have provided possible explanations for the lack of significant statistical evidence of progesterone effectiveness.

It is now obvious that original dosages were virtually homoeopathic* and it has also been shown that the selection of trial groups has been unscientific and that the statistical methods of Malpas used in establishing the probability of miscarriage are unacceptable (Goldzieher,† Swyer‡) Repeated biopsies in the aborters with a distinctly underdeveloped secretory endometrium have demonstrated that once in every 3 to 4 cycles these same patients will present a normal secretory endometrium (Grant§) and it is a natural assumption that any therapy coinciding with a pregnancy arising in such a cycle will receive the credit It is now acceptable, on grounds of sound clinical evidence backed by controlled trials, that progesterone deficiency during the secretory phase and during the first trimester is responsible for the major part of early miscarriages. The work of Kupperman,* using pregnanediol estimations and Grant, using preconception

* Swyer, G I M., *Brit Med J*, 5081 1297 (1958).
† Goldzieher, J. W, *Amer J Obstetr. Gynec* 75, 6 1202 (1958)
‡ Swyer *et al* *Brit. Med J*, 4819 1073 (1953)
§ Grant, Alan, *Intern J Fert* 4, 4 323 (1959)
* Epstein, J A, Kupperman H S, & Cutler, A, *Ann New York Acad Sc*, 71, 5 560 (1958)

based on the observation that, in women of normal fertility in whom this type of therapy is employed for oral contraception, the fertility rate appears to be increased after cessation of therapy.

Dosage Anovlar (4 mg. N.E.A. + 0·05 mg. ethinyl oestradiol): 1 dragee daily from the 5th to 25th day of the cycle.

ABORTION

The termination of pregnancy before 28 weeks is termed abortion and in relation to hormone therapy, may be classified into two major groups: (1) Threatening; (2) Habitual.

Threatening Abortion

Here the cervical os is closed and the stage is characterised by uterine bleeding, usually with contractions. At this point therapy is possible to assist in avoiding abortion during early pregnancy, but this phase is generally transient and the patient should settle down relatively quickly under appropriate treatment (which includes rest and sedation as well as specific hormone therapy) or will proceed to the stage of "starting abortion" or "inevitable abortion", where the cervical os is dilated and placental separation is past being influenced.

Since uterine contractions at this stage are generally not influenced by treatment, the abortion is then either a "complete" or an "incomplete" abortion (where the placenta is retained and a curette is necessary). Curettage is generally also indicated in a "missed abortion", where the foetus is dead but not expelled In a large percentage of cases foetal abnormality and death *in utero* precedes the threatening stage Of those cases where there is a normal, live foetus, many will have reached the inevitable stage before treatment can be instituted Because of the difficulty of assessing between threatening and starting abortion and the relatively low percentage of foetuses that can be salvaged, the results of treatment are variable

Hormone therapy in threatening abortion is therefore a controversial subject. However, there is definite evidence of benefit from progesterone therapy and the use of such therapy, particularly in cases exhibiting a low pregnanediol excretion, has been shown to be statistically sound (Goldzieher*) Since pregnanediol

* Goldzieher *Amer J Obst Gynec* 75, 6 1202 (1958)

Other Causes Not Suitable for Hormone Therapy

Incompetent Cervix—Is a cause of habitual abortion, particularly those occurring after the 4th month. This condition can be diagnosed by characteristic history, by special examination technique and/or X-ray examination.

Malformation of the Uterus—uterine fibroids or—fixed retroversion of uterus by limiting uterine growth and thus causing pressure and final expulsion of foetus, usually from the 2nd to 4th months. Fixed retroversion of uterus and other acquired pelvic pathology (except pelvic inflammatory disease with or without fibroids) as the proven cause of an abortion, is comparatively rare.

Genetic Foetal Abnormalities—As with threatening abortion, it is possible that genetic abnormalities may lead to recurrent abortion and this factor may explain the difficulty encountered in producing better than 80 per cent salvage rate in habitual abortion.

Systemic Disease—e.g., chronic intoxication, etc.

Progestogens and the Foetus

As pointed out in the section dealing with virilisation, iatrogenic virilisation of the female foetus may be induced by the administration of a number of steroids to the pregnant woman. Animal experiments have shown that virtually all the currently available progestogens are capable of producing androgenic effects in the female foetuses of rats. In clinical practice, congenital virilisation (limited to clitoral enlargement and fusion of the labia) has been reported in a very small percentage of female neonates whose mothers have received androgens, oestrogens, natural progesterone and principally synthetic progestogens during the early weeks of pregnancy. These changes have also occurred in cases where no steroids have been administered and are possibly related to some idiosyncrasy of maternal endocrine metabolism. Despite the fact that they are relatively rare and readily corrected, the use of suspect steroids is now contraindicated during early pregnancy.

Note: It should be emphasised that in this respect hydroxyprogesterone capronate (Proluton-Depot) has been shown to be devoid of undesirable effects by both experimental studies and wide clinical usage.

and 100-day postconception basal body temperature graphs, confirms that diminished progesterone production is a definite factor in recurrent abortion and that adequate and early treatment with progestogens in this type of aborter should result in an increase in pregnancies carrying to term

Habitual abortion means a history of three or more consecutive abortions in the patient. Every effort should be made to ascertain the cause.

Endocrine Causes of Habitual Abortion

Progesterone Deficiency

At the time the placenta should take over production of progesterone, a progesterone deficiency from too early withdrawal of corpus luteum production or delay in placental production may be the cause of abortion at the 12th to 14th week.

Dosage Proluton-Depot (hydroxy-progesterone-capronate): 250-500 mg. i.m. weekly, administered as early as possible in pregnancy and maintained over first half of pregnancy or for four weeks past longest unsuccessful gestation (whichever is longer)

Faulty Nidation

This results, generally, in early abortion (i.e. in the first trimester) or infertility due to failure of nidation. Evidence has been adduced that in patients with a history of two, three or four previous abortions, over 60 per cent show abnormal and/or weak secretory transformation of endometrium. In such cases, preconception treatment aimed at providing adequate secretory changes, is usually the therapy of choice

Preconception Therapies

(a) *Proluton-Depot (hydroxy-progesterone-capronate):* 125 mg intramuscularly on 18th day of cycle and when there is absence of menstruation indicating conception, continue for the first half of pregnancy at weekly intervals using 250-500 mg Proluton-Depot

(b) Primolut-N (nor-ethisterone) *5 mg orally b i d. (twice daily) from the 18th to 25th day of cycle Further treatment require*ments are assessed by basal temperature chart and, if the patient becomes pregnant, transfer to weekly injections of 250-500 mg of Proluton Depot, for first half of pregnancy

Causes of Amenorrhoea

1. *Normal or Physiological*—pregnancy—lactation—menopause—silent cycle.
2. *Non-endocrine*
   (a) Congenital Anatomical Defects: absence of genitalia—imperforation along the genital tract—endometrial defects.
   Acquired Anatomical Defects: castration—post abortum debris—endometrial atresias or atrophy—harsh curettage
   (b) Systemic· chronic debilitating diseases—blood dyscrasias—severe dietary deficiencies—intoxications—obesity—trauma.
   (c) Psychogenic: emotional factors—environmental circumstances—shock.
3 *Endocrine*
   (a) Thyroid Dysfunction. hyperthyroidism—hypothyroidism.
   (b) Virilising Syndromes adrenal and ovarian in origin
4. *Functional*

(For the purposes of this text the term "functional" relates to endocrine activity along the hypothalamic-pituitary-ovarian axis)

   (a) Hypothalamic Level—neurogenic interference arising from local or proximal intracranial lesions. The hypothalamus might also be regarded as the level through which systemic and psychogenic factors exert their effect
   (b) Pituitary Level—pituitary dysfunction may be—
      (1) Primary failure or deficiency of gonadotropins
      (2) Primary failure or deficiency of tropic hormones generally (panhypopituitrinism)
      (3) Hypofunction secondary to hypothalamic direction
   (c) Ovarian Level—ovarian dysfunction may be—
      (1) Primary failure.
      (2) Secondary to pituitary hypofunction
      (3) Follicular hyperfunction.

PRIMARY AMENORRHOEA

The prognosis in primary amenorrhoea is dependent upon the cause and since the role of sex hormone therapy, in all indications, is restricted to "functional" disturbances, all other possible

HORMONE THERAPY IN MENSTRUAL CYCLE DISTURBANCES

Definitions—Owing to the confusion that prevails in existing terminology as applied to disturbances of menstruation, in particular the uterine bleedings, an attempt has been made to simplify classifications. Disturbances of menstrual bleeding fall, naturally, into major groupings and in order to avoid misinterpretation of terms, the following definitions have been adopted:

No Menstruation

Amenorrhoea—the complete absence of menstruation.

Too Little Menstruation

Hypomenorrhoea—scanty menstruation at normal cyclical intervals.

Oligomenorrhoea—scanty menstruation at extended intervals.

Too Many Menstruations

Polymenorrhoea—shortened regular intervals between menstruations

Bleeding at Ovulation—regular mid-cycle bleeding

Too Much or Excessive Menstruation

Hypermenorrhoea and Menorrhagia—excessive menstruation at normal cyclical intervals but of prolonged duration or amount

Premenstrual Spotting—irregular bleeding during the premenstruum.

Metrorrhagia—non-cyclic or irregular uterine haemorrhage. All non-cyclic excessive uterine bleeding is included under this term

Numerous other terms exist that are synonymous with some of the foregoing, but these have been discarded in order to avoid confusion

AMENORRHOEA

Amenorrhoea is defined as a complete absence of menstruation and may be (a) *primary, where the patient has never previously* menstruated or (b) secondary, where there is failure of menstruation in a previously menstruating woman

Treatment of Functional Disturbances

As the severity of the underlying "functional" causes would indicate, the prognosis in true primary amenorrhoea is poor and endocrine therapy aimed at inducing spontaneous ovulatory cycles will fail in approximately 80 per cent of cases. There are a number of cases in which amenorrhoea reflects a "delayed menarche" or fault that is minor rather than a true primary failure and these no doubt constitute the bulk of those in whom a complete response might be expected

Provided the endometrium is capable of response and the uterus reasonably developed, appropriate hormone therapy will consistently induce a "menstrual-like" bleeding At the same time, it is possible to correct the sexual and general infantilism that is common to primary amenorrhoea. In this respect, the psychological and physical benefits that can be produced and maintained by hormone therapy warrant its application even though the institution of normal cycles is not possible. Where investigations or absence of obvious symptoms indicate that no major disturbance is involved, treatment should be delayed until the 18th year in order to allow for a delayed menarche

Developmental Therapy

Primary amenorrhoea is usually associated with genital underdevelopment and where this is marked, development therapy should first be instituted Several methods are available for correcting uterine hypoplasia

1 Cyclical oestrogen therapy
2 Pseudo-pregnancy therapy
3. Direct injection therapy

Dosage For dosage see "Uterine Hypoplasia", p 75

Substitution Therapy

When adequate development has been achieved, therapy should be *aimed at institution of a cyclical response by substitution of* normal steroid requirements In the presence of a responsive endometrium, this will induce a withdrawal bleeding and the cyclical fluctuation of steroid levels will at the same time provide a feedback stimulus to the pituitary-ovarian axis The therapy should be repeated over 3 or 4 cycles after which a period is

factors must first be eliminated. It is of particular importance, where amenorrhoea is associated with sexual infantilism, that hormone therapy be avoided until a diagnosis is reached The sexual maturation artificially achieved with exogenous hormones may render subsequent diagnostic efforts difficult.

Causes

1. *Normal*—Conception in the first cycle is the only possible normal cause but is an extremely unlikely factor in primary amenorrhoea.
2. *Non-endocrine*—all aspects of this group are applicable to primary amenorrhoea with the exception of acquired anatomical defects and possibly psychogenic factors.
3. *Endocrine*—To be applicable to primary amenorrhoea, thyroid dysfunction and virilising syndromes would more likely be congenital in nature
4. *Functional*
   (a) Hypothalamic—Apart from local lesions (Fröhlich's syndrome) which are very rare, the hypothalamus is an unlikely site of primary interference.
   (b) Pituitary—Primary pituitary deficiency is a relatively common and frequently intractable factor, usually arising from marked disturbances (trauma, tumours, haemorrhage, infection, etc.) and frequently extending to panhypopituitrinism The resultant loss of anterior pituitary function is reflected in many organs other than gonads as in Simmond's disease, Lorraine dwarfism etc A selective deficiency of gonadotropins is probably much less common except in "delayed menarche" Pituitary deficiency may be differentiated by the accompanying low levels of excreted gonadotropins or by a positive response of ovaries to administered gonadotropins
   (c) Ovarian—Primary failure of the ovaries is also a relatively common and usually intractable cause of primary amenorrhoea Not infrequently it is associated with congenital maldevelopment such as gonadal dysgenesis (Turner's syndrome) Steroid excretion levels are invariably low when the ovary is involved while gonadotropin excretion is high.

The loss of previously existing menstruation may be of short duration (under 12 months) or long duration and shares many of the causative factors that contribute to primary amenorrhoea. There are, however, some distinct differences and these have a direct bearing on the prognosis.

1. **Normal**—Pregnancy is the most common cause of short duration secondary amenorrhoea—menopause is the most common cause of long duration secondary amenorrhoea—lactational amenorrhoea is self-evident but pregnancy and menopause should never be overlooked

2 **Non-endocrine**—All aspects are applicable to secondary amenorrhoea excepting congenital anatomical defects—psychogenic factors are extremely common and along with pregnancy constitute all but a small percentage of short duration cases

3 **Endocrine**—More likely than in primary amenorrhoea but relatively rare.

4 **Functional**

(a) Hypothalamus—Extremely common as a site of interference secondary to all the above factors except anatomical.

(b) Pituitary—Pituitary deficiency is relatively rare and applies also to secondary amenorrhoea but again usually involves extensive and intractable disruption leading to permanent amenorrhoea associated with distinctive syndromes (Simmond's disease, or Sheehan's syndrome, acromegaly, Cushing's disease, Chiari-Frommel syndrome etc)

(c) Ovarian—A primary ovarian deficiency may develop during sexual maturity (tumours, Stein-Leventhal syndrome, premenopause, and menopause) leading to secondary amenorrhoea More commonly in juveniles and women over 35, however, a hyperfunction of follicular production (persistent follicles) leads to "hyper-hormonal" amenorrhoea (see Metrorrhagia, p 96)

Treatment

As may be seen from the list of functional causes the more rare, extensive primary disturbances of the pituitary and ovary are

allowed for observation. In the event of the cycle failing to continue spontaneously, the regime may be repeated.

Dosage Primogyn-Depot (oestradiol valerianate): 10 mg. i.m. on the first day

followed by

Primogyn-Depot (oestradiol valerianate): 10 mg. i.m combined with Proluton-Depot (hydroxy-progesterone-capronate): 250 mg. i m.	on the 14th day of treatment

Oral Alternative Primogyn-C (ethinyl oestradiol)· 0·02 mg t.d s from the first to 23rd day after starting therapy

combined with

Primolut-N (nor-ethisterone). 5 mg. thrice daily from 14th to 23rd day

Stimulation Therapy

Subsequent to failure of substitution therapy or where it has already been decided that the fault is ovarian, direct stimulation of the ovaries may be undertaken (see also Anovulatory Cycles, p 76)

As mentioned previously, direct gonadal stimulation may be attempted with P.M S and H C G. administered in a normal cyclical fashion over several months followed by a period of observation

Dosage Primantron (F S.H.): 1,000 i u i m every third day, i e 3rd, 6th, 9th, 12th, 15th, 18th days,

together with

Primogonyl (L H.). 1,000 i u. i m. every second day, i e. 12th, 14th, 16th, 18th days.

When endocrine assays of gonadotropins and ovarian steroids are not possible, the foregoing therapies may also be employed in order to differentiate between failure at the pituitary, ovarian, or end organ level.

Where it is obvious from initial investigations or subsequent trial of hormone therapy that an intractable failure is present, maintenance of the patient on the substitution therapy is recommended

SECONDARY AMENORRHOEA

The loss of previously existing menstruation may be of short duration (under 12 months) or long duration and shares many of the causative factors that contribute to primary amenorrhoea. There are, however, some distinct differences and these have a direct bearing on the prognosis.

1. Normal—Pregnancy is the most common cause of short duration secondary amenorrhoea—menopause is the most common cause of long duration secondary amenorrhoea—lactational amenorrhoea is self-evident but pregnancy and menopause should never be overlooked.

2. Non-endocrine—All aspects are applicable to secondary amenorrhoea excepting congenital anatomical defects—psychogenic factors are extremely common and along with pregnancy constitute all but a small percentage of short duration cases.

3. Endocrine—More likely than in primary amenorrhoea but relatively rare

4 Functional

(a) Hypothalamus—Extremely common as a site of interference secondary to all the above factors except anatomical

(b) Pituitary—Pituitary deficiency is relatively rare and applies also to secondary amenorrhoea but again usually involves extensive and intractable disruption leading to permanent amenorrhoea associated with distinctive syndromes (Simmond's disease, or Sheehan's syndrome, acromegaly, Cushing's disease, Chiari-Frommel syndrome etc)

(c) Ovarian—A primary ovarian deficiency may develop during sexual maturity (tumours, Stein-Leventhal syndrome, premenopause, and menopause) leading to secondary amenorrhoea. More commonly in juveniles and women over 35, however, a hyperfunction of follicular production (persistent follicles) leads to "hyper-hormonal" amenorrhoea (see Metrorrhagia, p 96)

Treatment

As may be seen from the list of functional causes the more rare, extensive primary disturbances of the pituitary and ovary are

associated with secondary amenorrhoea of long duration. Treatment and prognosis are therefore identical with primary amenorrhoea. In contrast, the causes allied with amenorrhoea of short duration are principally related to reversible effects acting through the hypothalamus. Prognosis in such cases is therefore excellent and failure to respond to therapy is indicative of pregnancy or one of the more deep seated causes. In this condition, it is possible to eliminate the most common cause (pregnancy) and treat the functional disturbance in the one step by utilising the "withdrawal effect".

The administration and withdrawal of appropriate amounts of a progestogen and oestrogen will induce a bleeding from a responsive endometrium and this will be sufficient to overcome the temporary interruption that exists at the hypothalamic level in the vast majority of cases. If pregnancy is present, however, endogenous production of hormones will already be too high to permit withdrawal

Dosage Duogynon Simplex (50 mg progesterone + 3 mg oestradiol benzoate in 1 c.c. disposable syringe)—one i.m. injection, or

Duogynon (20 mg. progesterone + 2 mg oestradiol benzoate in one 1 c.c. ampoule) one i.m. injection for two consecutive days.

Oral Alternative Duogynon Oral (10 mg nor-ethisterone acetate + 0 02 mg ethinyl oestradiol): 1 dragee on two consecutive days

In functional disturbances a menstrual-like bleeding should occur approximately 2 to 4 days after cessation of the above therapies Such a bleeding is usually sufficient to lead to reinstitution of regular menstruation and simultaneously provides a 100 per cent reliable negative pregnancy test Conversely an absence of a bleeding which approximates normal menstruation provides a 95 per cent reliable positive pregnancy test.

HYPOMENORRHOEA

Hypomenorrhoea is defined as scanty menstruation occurring at normal cyclic interval It may stem from any of the causes listed for secondary amenorrhoea, but since normal fertility and

health are quite compatible with scanty menstruation, a variation in endometrial response is probably a major factor.

The fact that hypomenorrhoea (or any menstrual disturbance) is a symptom and might reflect one of the more serious causative factors should not be overlooked, but treatment of this condition in otherwise normal women is unnecessary.

OLIGOMENORRHOEA

Oligomenorrhoea is also a scanty bleeding but one that occurs at extended intervals. Although it can also be compatible with normal health and fertility, a frequent association with anovulatory intervals and consequent infertility, together with the fact that it could be classified as a sub-species or precursor of amenorrhoea, renders it much more significant than hypomenorrhoea Irrespective of whether treatment is undertaken or not, it should always be considered as a possible indication of serious causative factors

Causes

Other than "functional", all causes listed for secondary amenorrhoea may be applied, particularly virilisation and obesity, which are often associated with oligomenorrhoea and concomitant infertility

Functional—Oligomenorrhoea is typified by extension of the proliferative phases and infrequent ovulation succeeded by relatively normal secretory phases. This might be explained by:

(a) Primary follicular insufficiency

(b) Follicular insufficiency secondary to pituitary hypofunction.

Treatment

Oligomenorrhoea of "functional" origin is prone to occur following the menarche and during the premenopausal period and at these transitional stages does not necessarily require treatment "Functional" disturbances that persist in the juvenile or are present in the sexually mature patient warrant treatment. Since infertility arising from anovulatory states is the principal cause for complaint in oligomenorrhoea, hormone therapy follows the lines set out under "anovulatory cycles" (p 83) and "pseudo-pregnancy" is the therapy of choice As

the ovary is capable of occasional ovulation the prognosis is significantly better and the rationale for this therapy is supported by observations that women with this complaint often show marked improvement after having achieved pregnancy.

Dosage An eight weeks course as follows:
Primogyn Depot (oestradiol valerianate): 10 mg i m. weekly for the first 4 weeks and increasing to 20 mg. i m. weekly for the second 4 weeks together with:

Proluton Depot (hydroxy-progesterone-capronate): 125 mg. i m weekly for the first two weeks and increasing by 125 mg each fortnight.

The effect of this therapy produces (a) amenorrhoea for the duration of the therapy; (b) rapid stimulus to uterine growth; (c) strong withdrawal bleeding after cessation of therapy followed by a short interval of amenorrhoea; (d) the recurrence of menstrual cycles, often with ovulation and a more normal pattern.

As an alternative, the other methods outlined for anovulatory cycles may be employed and where freedom from pregnancy is desired, contraception and simultaneous provision of regular menstruation can be achieved by cyclical use of norsteroids.

Dosage Anovlar (4 mg. N.E.A. + 0 05 mg. ethinyl oestradiol): 1 dragee daily from the 5th day to the 25th day of the cycle

POLYMENORRHOEA

Polymenorrhoea may be defined as a regular shortening of the cycle and menstruation occurring at intervals less than 25 days must fall within this category, provided the interval is regular Where the span between bleedings approaches 14 days, care must be taken to exclude the possibility of bleeding at ovulation (see p. 92) or the rarer possibility of a regular metropathia haemorrhagica (see p 96)

Causes

Although the regularity of the shortened cycle would tend to exclude "non-functional" causes, pelvic lesions and inflammations should not be overlooked In the vast majority of cases, however,

the causative factor is most likely a functional disturbance at the ovarian level and may take one of three forms:

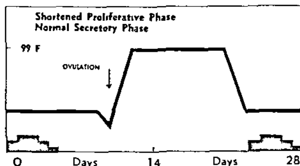
(a) Premature follicular maturity—giving rise to early ovulation and shortening of the proliferative phase

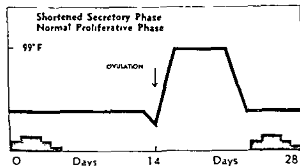
(b) Premature corpus luteum regression—giving rise to a shortened secretory phase.

(c) Failure of ovulation—giving rise to an oestrogen withdrawal and complete absence of a secretory phase.

Treatment

In cases where the variation from normality is not great, treatment is not necessarily indicated. In others, marked inconvenience, excessive blood loss and resultant infertility may necessitate action. Although it is possible to achieve a normal cycle length by delay of menstruation with progestogens in each of the three forms, an attempt should be made to determine which is responsible. The most convenient method for assessing this point is the basal body temperature graph





the ovary is capable of occasional ovulation the prognosis is significantly better and the rationale for this therapy is supported by observations that women with this complaint often show marked improvement after having achieved pregnancy.

Dosage An eight weeks course as follows:
Primogyn Depot (oestradiol valerianate): 10 mg. i.m. weekly for the first 4 weeks and increasing to 20 mg. i m. weekly for the second 4 weeks together with:

Proluton Depot (hydroxy-progesterone-capronate): 125 mg. i m. weekly for the first two weeks and increasing by 125 mg. each fortnight.

The effect of this therapy produces (a) amenorrhoea for the duration of the therapy; (b) rapid stimulus to uterine growth; (c) strong withdrawal bleeding after cessation of therapy followed by a short interval of amenorrhoea; (d) the recurrence of menstrual cycles, often with ovulation and a more normal pattern.

As an alternative, the other methods outlined for anovulatory cycles may be employed and where freedom from pregnancy is desired, contraception and simultaneous provision of regular menstruation can be achieved by cyclical use of norsteroids

Dosage Anovlar (4 mg. N E A. + 0·05 mg. ethinyl oestradiol): 1 dragee daily from the 5th day to the 25th day of the cycle.

POLYMENORRHOEA

Polymenorrhoea may be defined as a regular shortening of the cycle and menstruation occurring at intervals less than 25 days must fall within this category, provided the interval is regular Where the span between bleedings approaches 14 days, care must be taken to exclude the possibility of bleeding at ovulation (see p. 92) or the rarer possibility of a regular metropathia haemorrhagica (see p 96)

Causes

Although the regularity of the shortened cycle would tend to exclude "non-functional" causes, pelvic lesions and inflammations should not be overlooked In the vast majority of cases, however,

Causes

Such bleeding is probably the result of a normal endometrial response following a sharper decline than is usual in the oestrogen level succeeding ovulation or a more sensitive endometrial response to the normal postovulatory decline. Generally the patient will complain of a "menstruation" every 14 days, and if the inter-menstrual bleeding is of sufficient extent it may possibly give rise to infertility and anaemia, apart from inconvenience to the patient.

Treatment

The condition must not be confused with polymenorrhoea or metrorrhagia, the most significant feature of ovulatory bleeding being the regularity of bleeding every 14 days (in a 28-day cycle) The practitioner must determine which bleeding is the true menstruation, by means of a basal body temperature graph or endometrial biopsy, before undertaking treatment.

Ovulatory bleeding *per se* does not often warrant treatment but where the duration is sufficiently protracted and the amount of blood loss excessive, therapy is indicated. Oestrogen therapy is administered, at the time of ovulation, to offset the withdrawal of naturally occurring oestrogen at this point in the cycle

Dosage Progynon B Oleosum Forte (oestradiol benzoate)· 5 mg i m injection administered one to two days before ovulation or before the onset of the ovulatory bleeding.

This therapy should give an immediate result, but a second injection after an interval of two days may be required in some patients Subsequent cycles should be similarly treated over a period of six months

Alternative Dosage Where avoidance of pregnancy is desired, concurrent contraception and correction of bleeding can be achieved by suppression of ovulation

Anovlar (4 mg nor-ethisterone acetate + 0·05 mg ethinyl oestradiol): 1 tablet daily between the 5th and 24th days of the menstrual cycle (counting the first day of true menstruation as day one)

HYPERMENORRHOEA AND MENORRHAGIA

Excessive menstruation at normal cyclical interval may be abnormal in amount (hypermenorrhoea) or in duration (menorrhagia). For all clinical purposes both entities may be grouped under

(a) Premature Follicular Maturity (short proliferative phase) By retarding maturation of the Graafian follicle, ovulation may be postponed and the cycle lengthened This may be achieved by administering oestrogens early in the cycle in order to reduce F.S H. output.

Dosage Progynon B Oleosum Forte (oestradiol benzoate). 5 mg i.m ampoules. One *injection (1 to 2 ampoules) is given between* the 4th and 6th days of the menstrual cycle This regime should be repeated for several cycles.

(b) Premature Luteal Regression (short secretory phase) Early regression of corpus luteum production may be off-set by administering a progestogen, thus preventing the normal withdrawal effect and the concomitant desquamation of the endometrium

Dosage Primolut-N (nor-ethisterone): 5 mg. tablets two to three times daily is commenced two days before the expected date of menstruation and continued daily until three days prior to the desired date of menstruation

(c) Anovulatory cycles.
As previously pointed out, induction of ovulation is difficult and should be undertaken as set out on p. 76

Alternative Method In those ovulatory cases where avoidance of pregnancy is desired, provision of regular cycles of normal duration with concurrent contraception can be achieved
Dosage Anovlar (4 mg N.E.A + 0·05 mg ethinyl oestradiol) one dragee daily from the 5th to the 25th day of each cycle

Delay of Normal Menstruation

The principle and dosage applied to premature luteal regression can be extended to normal physiological cycles Such treatment may be indicated prior to surgical operations or for sporting and social reasons In these cases postponement of menstruation should be limited to one week

BLEEDING AT OVULATION

Bleeding at ovulation is a rare condition where endometrial breakdown occurs immediately following ovulation. The bleeding may be in the form of spotting or a more substantial menstrual like flow of two to three days' duration

2. Luteal persistence—too gradual a decline or persistence of luteal production after initial withdrawal could result in a slow clearance of threshold values and consequent extension of menstrual flow and duration
3. Luteal failure—failure of ovulation may in some cases lead to hyperproliferation of the endometrium and excessive bleeding at cyclical intervals. However, anovulatory excessive bleedings are much more likely to be irregular in nature (see Metrorrhagia, p. 96)

Treatment

Dosage Testoluton Forte (ampoules containing 25 mg testosterone propionate + 10 mg. progesterone) i m injection daily for 3 days during menstruation.

Prophylaxis—This is generally undertaken with a progestogen in order to induce an adequate secretory transformation of the endometrium and to ensure a correctly timed and sharply defined withdrawal effect. Of the various progestogens available, the norsteroids have proved highly effective and are the substances of choice.

Dosage Primolut-N (nor-ethisterone) 5 mg b d. from the 18th to the 25th day of the cycle

Alternative Dosage Where avoidance of pregnancy is desired, marked control of menorrhagia with concurrent contraception can be

Anovl. 1 dragee daily f

Menorrhagia from Fibroids

Although it has so far been emphasised that hormone therapy has no application to causative factors that are not "functional",

the fibroids or reduce the frequency of menstrual symptoms but will control occurring haemorrhage until more appropriate action can be taken.

menorrhagia. The fact that these excessive bleedings follow a regular cyclical pattern indicates that ovulation usually occurs in these cycles and the term "ovulatory menorrhagia" is consequently applied.

Causes

1. *Non-endocrine*

   (a) Congenital Anatomical Defects—uterine hypoplasia resulting in interference with contractions—maldevelopment creating a greater bleeding area
   Acquired Anatomical Defects—factors leading to interference with contractions (intramural fibroids, fibrosis uteri, atony)—factors affecting endometrial healing (inflammations, post-abortum and post-partal debris)—venous congestion (fixed retroflexure)

   (b) Systemic—disturbances of blood chemistry (dyscrasias, anaemias, leukemia, clotting defects)—hypertension

   (c) Psychogenic—emotional factors may possibly contribute to increased menstrual loss.

2. *Endocrine*—Hypothyroidism.

3 *Functional*

As outlined in the section dealing with menstruation, adequate luteal production of progesterone, followed by rapid decline through an optimal threshold, is required for a normal clear cut desquamation. A not uncommon finding in cases of ovulatory menorrhagia is an inappropriate or "mixed" histological picture in the endometrium; suggestive of a functional disturbance

   (a) Hypothalamic Level—interference here is unlikely except in response to psychogenic factors

   (b) Pituitary Level—unlikely as a primary site of interference

   (c) Ovarian Level—a disturbance of the ovary appears to be the most likely functional factor and might be as follows:

      1. Luteal insufficiency—resulting in a poor secretory transformation of the endometrium and faulty desquamation

2 Luteal persistence—too gradual a decline or persistence of luteal production after initial withdrawal could result in a slow clearance of threshold values and consequent extension of menstrual flow and duration.

3. Luteal failure—failure of ovulation may in some cases lead to hyperproliferation of the endometrium and excessive bleeding at cyclical intervals However, anovulatory excessive bleedings are much more likely to be irregular in nature (see Metrorrhagia, p 96)

Treatment

Immediate—For rapid hae

effective but oestrogen is

a "relative hyperoestrinism

progestogens have a styptic effect and are synergistic in their action on the endometrium, this combination is chosen

Dosage Testoluton Forte (ampoules containing 25 mg testosterone proprionate + 10 mg progesterone) i m injection daily for 3 days during menstruation

Prophylaxis—This is generally undertaken with a progestogen in order to induce an adequate secretory transformation of the endometrium and to ensure a correctly timed and sharply defined withdrawal effect. Of the various progestogens available, the norsteroids have proved highly effective and are the substances of choice

Dosage Primolut-N (nor-ethisterone) 5 mg b d from the 18th to the 25th day of the cycle

Alternative Dosage Where avoidance of pregnancy is desired, marked control of menorrhagia with concurrent contraception can be achieved through suppression of ovulation

Anovlar (4 mg. N E A + 0·05 mg ethinyl oestradiol). 1 dragee daily from the 5th to 25th day of each cycle

Menorrhagia from Fibroids

Although it has so far been emphasised that hormone therapy has no application to causative factors that are not "functional",

the fibroids or reduce the frequency of menstrual symptoms but will control *occurring haemorrhage until more appropriate* action can be taken

METRORRHAGIA

Metrorrhagia includes all irregular (non-cyclic) forms of uterine bleeding. The erratic nature of these haemorrhages which are frequently prolonged and excessive, constitutes a significant distinction between metrorrhagia and cyclical forms of excessive uterine bleeding since it is either indicative of an anovulatory functional disturbance or may reflect the presence of serious pelvic lesions.

Causes

1. *Non-endocrine*
   (a) Acquired Anatomical Defects—genital carcinoma—fibroids—polyps—endometrial inflammations—cervical erosion.
   (b) Systemic—disturbances of pregnancy (ectopic pregnancy—threatened abortion)—blood dyscrasias
   (c) Psychogenic.
2. *Endocrine*
   (a) Hypothyroidism.
   (b) Stein-Leventhal syndrome may occasionally be associated with metrorrhagia but more commonly causes amenorrhoea
3. *Functional*

Follicular Hyperfunction—In this entity a disturbance of feed-back mechanism or ovarian response results in an anovulatory state in which the activity of a Graafian follicle or succession of follicles persists (persistent follicles). The continued influence of elevated oestrogen levels and absence of luteal effects produce a hyperproliferation of the endometrium which is distinguished by marked cystic development of the glands (cystic glandular hyperplasia). A preliminary state of amenorrhoea (hyperhormonal amenorrhoea) accompanies the development of endometrial hyperplasia but subsequent fluctuations in oestrogen levels, as follicles regress and are replaced, produce intervals of profuse bleeding (metropathia haemorrhagica) interspersed with erratic periods of lesser bleeding and amenorrhoea. As might be expected, there is a relationship between the stage of sexual maturity and the relative incidence of "functional" and other causes as illustrated by the following table

In Juveniles	Incidence as cause of metrorrhagia %
1. Functional	60
2 Threatened abortion	20
3. Inflammation	10
4. Systemic diseases	10
In the Sexually Mature	
1 Threatened abortion	40
2 Carcinoma 3. Fibroids	30
4. Inflammations	10
5 Functional	10
6. Systemic diseases	10
In the Premenopausal	
1. Carcinoma	35
2. Functional	35
3 Fibroids	10
4 Inflammations 5. Cervical erosion 6 Systemic diseases	20

Treatment

The response of metropathia haemorrhagica to endocrine therapy is most rewarding It should be stressed that although certain non-functional causes call for radical methods of treatment, the use of surgical techniques (particularly hysterectomy) is seldom if ever indicated for "functional" disturbances However, the association between irregular uterine haemorrhage and serious pelvic lesions renders correct diagnosis mandatory The age of the patient is often an important factor in diagnosis but full confirmation and elimination of malignancy as a cause can only be achieved by curettage Although curettage is a temporary effective therapeutic measure in a percentage of cases its prime application in this indication should be as a diagnostic procedure

Juveniles

Curettage is generally undesirable, particularly where rupture of the hymen is involved Nevertheless a thorough *per vaginum* examination is necessary if disturbances other than ovarian are sus-

pected and if this is carried out under an anaesthetic, then diagnostic curettage is a logical step. However, the incidence of "functional" causes is so high in this group that it is safe to assume the presence of a metropathia and adopt endocrine therapy once threatening abortion has been ruled out.

Sexually Mature

When pregnancy disturbances have been eliminated, diagnostic curettage is desirable in this group. Where cystic glandular hyperplasia is confirmed, endocrine therapy may be adopted immediately or in subsequent recurrences.

Premenopause

In this group a diagnostic curettage is mandatory in order to exclude any possibility of genital carcinoma. Since it is not always possible to arrange for immediate hospitalisation, en*docrine therapy may be applied immediately provided curettage* is subsequently employed to confirm the diagnosis

Endocrine therapy in metropathia haemorrhagica is aimed at (a) immediate haemostasis, (b) medical curettage, (c) prophylaxis and possibly the induction of ovulatory cycles.

Immediate Dosage—Average Cases Primolut-N (nor-ethisterone); 5 mg tablets t d s for 10 days

Parenteral Alternative Primosiston (10 mg. oestradiol benzoate + 125 mg hydroxy-progesterone-capronate in 1 cc ampoule) 1 injection only.

These essentially progestational therapies will provide haemostasis within 24-48 hours in the vast majority of cases by virtue of a styptic effect together with a secretory transformation and maintenance of the endometrium A withdrawal bleeding (medical curettage) similar to a normal menstruation, should occur 8 to 10 days after Primosiston or 3 to 5 days after cessation of the oral regime This may vary according to the degree of endometrial loss when therapy is instituted

Immediate Dosage—Debilitated Cases Where a history of prolonged severe blood loss has led to a generally weakened condition of the patient or seriously affected the blood count, haemostasis over a more prolonged period may be desirable This may be achieved by uninterrupted continuation of the above oral therapy over the required interval Dependent upon the dura

tion and the tendency to "break-through" bleeding, it may be necessary to increase the daily dosage

Immediate Dosage—Continuous Bleeding *In certain cases the* continuous and obstinate nature of the bleeding may indicate a slightly altered situation in which bleeding continues from a bare basal plexus An initial proliferative therapy may be preferable under these circumstances

Progynon B Oleosum (oestradiol benzoate): 10 mg. plus Primogyn-Depot (oestradiol valerianate): 10 mg.	simultaneous i m injection

plus

Primogyn-Depot: 10 mg and Proluton-Depot (hydroxy-progesterone-capronate): 250 mg i m 14 days later.

Prophylactic Dosage Prophylactic therapy to prevent subsequent recurrence of endometrial hyperplasia should be undertaken until the functional disturbance has resolved itself or more specific steps to induce ovulatory cycles are introduced. The requirement of such therapy may be anticipated by use of the basal *body temperature chart and the use of an adequate progesta*tional dosage at suitably timed intervals will ensure clean des quamation of the endometrium.

Primolut-N (nor-ethisterone) 5 mg tablet b d. from the 23rd to 25th day of the proposed cycle as calculated from the first day of the medical curettage induced by the "immediate therapy"

Induction of Ovulation

T [illegible]

only in those rare cases which might be encountered during sexual maturity In the juvenile this disturbance is usually temporary in nature while the intervention of menopause will limit those cases where spontaneous resolution does not occur in the premenopausal group

DYSMENORRHOEA

Dysmenorrhoea is defined as painful menstruation and is a con*dition encountered to some degree in 50* per cent of *all* females It ranges in severity from mild discomfort to a severe and in-

pected and if this is carried out under an anaesthetic, then diagnostic curettage is a logical step. However, the incidence of "functional" causes is so high in this group that it is safe to assume the presence of a metropathia and adopt endocrine therapy once threatening abortion has been ruled out.

Sexually Mature

When pregnancy disturbances have been eliminated, diagnostic curettage is desirable in this group Where cystic glandular hyperplasia is confirmed, endocrine therapy may be adopted immediately or in subsequent recurrences.

Premenopause

In this group a diagnostic curettage is mandatory in order to exclude any possibility of genital carcinoma. Since it is not always possible to arrange for immediate hospitalisation, endocrine therapy may be applied immediately provided curettage is subsequently employed to confirm the diagnosis.

Endocrine therapy in metropathia haemorrhagica is aimed at (a) immediate haemostasis, (b) medical curettage, (c) prophylaxis and possibly the induction of ovulatory cycles.

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Immediate Dosage—Debilitated Cases Where a history of prolonged severe blood loss has led to a generally weakened condition of the patient or seriously affected the blood count, haemostasis over a more prolonged period may be desirable This may be achieved by uninterrupted continuation of the above oral therapy over the required interval Dependent upon the dura-

tion and the tendency to "break through" bleeding, it may be necessary to increase the daily dosage.

Immediate Dosage—Continuous Bleeding In certain cases the continuous and obstinate nature of the bleeding may indicate a slightly altered situation in which bleeding continues from a bare basal plexus An initial proliferative therapy may be preferable under these circumstances

Progynon B Oleosum (oestradiol benzoate): 10 mg plus Primogyn-Depot (oestradiol valerianate). 10 mg	simultaneous i m. injection

plus

Primogyn-Depot: 10 mg. and Proluton-Depot (hydroxy-progesterone capronate) 250 mg. i m 14 days later.

Prophylactic Dosage Prophylactic therapy to prevent subsequent recurrence of endometrial hyperplasia should be undertaken until the functional disturbance has resolved itself or more specific steps to induce ovulatory cycles are introduced. The requirement of such therapy may be anticipated by use of the basal body temperature chart and the use of an adequate progestational dosage at suitably timed intervals will ensure clean des quamation of the endometrium

Primolut-N (nor-ethisterone) 5 mg. tablet b d from the 23rd to 25th day of the proposed cycle as calculated from the first day of the medical curettage induced by the "immediate therapy"

Induction of Ovulation

[illegible]

only in those rare cases which might be encountered during sexual maturity. In the juvenile this disturbance is usually temporary in nature while the intervention of menopause will limit those cases where spontaneous resolution does not occur in the premenopausal group

DYSMENORRHOEA

Dysmenorrhoea is defined as painful menstruation and is a condition encountered to some degree in 50 per cent of all females It ranges in severity from mild discomfort to a severe and in-

capacitating pain and the more severe degrees might be expected in approximately 15 per cent of women.

This condition may be subdivided into two forms:

(a) Primary (true–functional–spasmodic). (b) Secondary

Primary Dysmenorrhoea

Primary dysmenorrhoea is not usually encountered until 2 to 3 years after the menarche. The pain is essentially uterine in origin and tends to be confined to the first day or two of menstruation

Causes

The causative factors underlying this condition are not clear and although a number of mechanisms have been suggested (myometrial ischemia, hypertonus or inco-ordinate activity) little is currently known of its aetiology. It appears to be related in some way to effects of progesterone since it occurs almost exclusively in ovulatory cycles and may sometimes be induced by exogenous progestogens. It is accepted that dysmenorrhoea is prone to exacerbation by psychogenic factors and prognosis is to an extent dependent on the degree to which spastic pain is overlaid by psychic apprehension

Treatment

The advent of e [illegible]
has provided a [illegible]
anovulatory cy [illegible]
symptoms in those cases which are primary in nature It might be expected that cessation of this type of therapy will lead to a recurrence of symptoms but due possibly to elimination of psychic factors, remissions tend to persist for some time in many cases

Dosage Anovlar (4 mg. N.E.A + 0·05 mg. ethinyl oestradiol) 1 dragee daily from the 5th to 25th day of the cycle Therapy should be repeated for 4 to 6 cycles after which the situation should be re-evaluated

Secondary Dysmenorrhoea

In secondary dysmenorrhoea the occurrence of pain tends to differ from that encountered in primary cases. In general the causative factor is some form of pelvic pathology and resultant pain is equally severe throughout menstruation and does not

usually occur until during sexual maturity In another form the pain is worse during the premenstruum with relief accompanying the onset of menses

Causes

(a) Acquired Anatomical Defects—endometriosis—fibroids—cervical stenosis
(b) Congenital Anatomical Defects—uterine hypoplasia
(c) Systemic—pelvic congestion

As with primary forms psychogenic exacerbation can be expected in secondary forms

Treatment

Anatomical defects should be treated as set out in the respective sections dealing with these complaints. Pelvic congestion appears to be only associated with that form of dysmenorrhoea which occurs during the premenstruum By virtue of its regular occurrence in this particular phase of the cycle it may be classified as part of a general premenstrual syndrome and its diagnosis is not infrequently confirmed by accompanying symptoms related to the syndrome (see p 102)

Dosage Primolut-N (nor-ethisterone) 5 mg tablets twice or thrice daily from the 18th to 25th day of the cycle

Juvenile Dysmenorrhoea

In the absence of regular ovulatory cycles it is unlikely that dysmenorrhoea in the juvenile patient will be primary in nature and as previously pointed out, it is not usual for primary dysmen*orrhoea to occur until 2 to 3 years after the menarche Similarly* it is unusual for secondary dysmenorrhoea stemming from ac*quired anatomical defects to arise until a reasonable stage of* sexual maturity has been achieved It is therefore more likely that the majority of these cases stem from pelvic congestion together with psychogenic exacerbation or as a result of uterine hypoplasia In such cases the appropriate endocrine therapies may be applied when the severity of the condition warrants treatment In the presence of regular ovulation, primary dysmenorrhoea might be assumed after other factors have been eliminated and suppression of ovulation, as previously outlined, may be undertaken In juveniles, however, this should be of a more restricted duration (2 or 3 cycles) and it is preferable that this regime be employed only where alternative measures (analgesics and spasmolytics) have proved of no avail

MITTELSCHMERZ

Mittelschmerz is a condition in which pain occurs at the time of ovulation and is common, from time to time, in approximately 50 per cent of all women. It is usually unilateral, mild and of short duration and is occasionally accompanied by slight vaginal spotting. It is not usual for patients to present for treatment except in the more severe cases However, it is possible for pelvic pain to be of sufficient severity and duration to necessitate treatment.

Causes

There appears to be a primary and a secondary form of mittelschmerz but although a number of theories have been suggested (tubal spasm, tension of the follicles etc.) the aetiology of the primary form is obscure and is possibly congenital in nature. Development of secondary mittelschmerz is frequently associated with pelvic lesions that cause difficulties in ovulation and consequent pain Endometriosis often gives rise to the development of this condition and the onset of ovulation pain in the sexually mature patient may be indicative of concomitant endometriosis

Treatment

In severe cases a thorough examination directed at the elimination of pelvic pathology is mandatory and hysterosalpingography, culdoscopy or laparotomy may be necessary to decide this factor Where the absence of pelvic lesions indicates the presence of the primary form, inhibition of ovulation in each cycle where remission of symptoms is desired will provide marked remission from symptoms and tend to reduce any psychogenic factors which may contribute to exacerbation.

Dosage *Anovlar (4 mg N E A + 0·05 mg ethinyl oestradiol) 1 dragee daily from the 5th to 25th day of each cycle*

Note. Where endometriosis is the causative factor, the same therapy may frequently be applied (see also Endometriosis, p 113)

PREMENSTRUAL SYNDROME

This syndrome is characterised by the repeated appearance of one or more of a number of symptoms during the week preceding menstruation The symptoms most commonly embraced by this syndrome are severe headache (often menstrual rather than premenstrual)—emotional psychic states (irritability, depression,

anxiety)—breast tension and pain—oedema—tachycardia—digestive disturbances.

However, the syndrome is so wide in its manifestations that any recurrent symptoms in the female patient should be checked against the menstrual calendar to ensure that they are not part of the premenstrual syndrome Symptoms that seem entirely unrelated to cyclical hormone influence but which have been demonstrated to be part of this syndrome,* are rhinorrhoea, rheumatism, nausea and vertigo, exacerbation of the skin, mucosal lesions, and asthma or epilepsy may also be related to the premenstrual phase. This syndrome is extremely common, particularly during the span of sexual maturity and affects approximately 60 per cent of all females Psychic tension is a marked feature and might vary from a mild form to marked states of anxiety or depression The influence of this aspect is recognisable in the fact that the bulk of all female crime, suicidal attempts and admissions to psychiatric institutions occurs during the premenstrual phase. The clinical diagnosis of premenstrual syndrome can be established with reasonable certainty from a case history which demonstrates the occurrence of symptoms related to the premenstruum

Causes

The true aetiology of premenstrual syndrome has not been established but the nature of certain symptoms, in particular breast pain and oedema, the cyclical nature of its recurrence and the tendency for this condition to occur at the premenopause is suggestive of an endocrine influence and clinical observation suggests the following functional causes

1 Systemic—Liver diseases by interference with degradation and excretion of oestrogen might possibly give rise to a form of hyperoestrinism

2 Ovarian Dysfunction—
   (a) Essential hyperoestrinism due to anovulatory cycles
   (b) Relative hyperoestrinism due to luteal insufficiency.

Treatment

Although the causative factors are not clear, clinical evidence would indicate that it is preferable to undertake therapy on the basis of assumed functional disturbances, rather than to apply

* Green, R , & Dalton K , *Brit Med J* 4818 1007 (1953)

symptomatic therapy to the separate entities which may be displayed. On this basis the general aim is to offset the oestrogen excess and the use of progestogens, whilst empirical, has proved extremely effective.†

Dosage *Primolut-N* (nor-ethisterone): 5 mg. tablets 2 to 3 times daily from the 18th to the 25th day of the cycle.

Where symptoms occur earlier, commencement of therapy should be appropriately advanced.

Alternative Dosage *Where it is desired to avoid pregnancy, remission of symptoms with concurrent contraception may be achieved by suppression of ovulation.*

Anovlar (*4 mg. N.E.A + 0·05 mg. ethinyl oestradiol*): 1 dragee daily from the 5th to 25th day of each cycle.

Note: The concomitant use of oral diuretics and restriction of salt intake may be employed to enhance the effect of the above therapies

Dosage Severe Cases—*in severe cases, particularly those with marked disturbance of psyche and where stimulus to psyche together with better control of oedema is required, the use of progesterone in combination with an androgen is preferable*

Testoluton (*testosterone proprionate 15 mg + progesterone 10 mg.*): 3 i.m. injections given at 3 day intervals commencing 10 days prior to menstruation

† Swyer, G. I. M., *Practitioner* 183 1091 211 (1959)

HORMONE THERAPY IN BREAST CONDITIONS

HORMONAL MASTOPATHIES

The occurrence of non-malignant changes in the epithelial and connective tissues of the breast, particularly as observed during the premenstrual phase, is classified under the general heading "mastopathies". These may be differentiated according to the severity of changes into 4 stages. There is a tendency for each of these stages to overlap and in most cases the latter classifications represent an extension of the previous phase or phases

[illegible]

7 to 10 days prior to menstruation, the onset of which provides remission of symptoms There are no palpable findings

2 *Chronic Interstitial Mastitis*—Chronic interstitial mastitis is also classified as fibro adenosis since there is painful involvement of the fibrous tissues, that leads to a diffuse nodularity, mainly in the upper outer quadrant of the breast (shotty breasts) There is also a chronic breast tenderness and all symptoms undergo premenstrual exacerbation

3 *Chronic Cystic Mastitis*—In this phase, which is also classified as fibrocystic disease, there is cystic involvement of the glands and ducts (ropy breasts) with increased proliferation of the epithelial tissues plus nodularity and cyst formation (lumpy breasts) While it is agreed that this condition is not pre-malignant, it has been estimated that 10% of these cases subsequently develop superimposed malignancy *†

4 *Involutionary Mastitis*—This is a cystic degeneration of the breast in which the formation of large cysts is accompanied by atrophic changes It has been estimated that 20% of this group develop superimposed malignant changes as well as the benign changes and the standard treatment is therefore surgery

Causes

The aetiology of these changes is rather obscure However, it is generally accepted that they represent either a normal response to a hyper oestrogenic effect or alternatively an exaggerated tissue

* Haagensen, S D "Diseases of the Breast" Saunders (1956)

† Cuningham, K & Wyse, E, *Med J Aust.* 46, 20 711 (1959)

response to circulating oestrogens. The administration of oestrogenic substances may in certain women produce parallel symptoms and if administered to women in whom this condition already exists, will usually give rise to exacerbation. It frequently occurs as part of the premenstrual syndrome, and ovarian dysfunction, leading to either essential or relative excess of oestrogen, may be assumed as common to both conditions (see causes, p 103).

Treatment

It should be emphasised that any lump in breasts should be regarded with suspicion and appropriate steps to eliminate the possibility of malignancy should always be undertaken In the past androgen therapy has been recommended but histological *evaluation* has shown little or no objective response to this type* [illegible] is difficult to demonstrate any [illegible] ovarian steroids, the applica- [illegible] the assumed basis of a relative oestrogen excess, has proved extremely effective in clinical practice and these results have been confirmed by double blind controlled trials.† Symptomatic relief is usually rapid and objective improvement can be achieved with continuation of the therapy. Adequate breast support should also be provided

Dosage *Premenstrual mastalgia and chronic interstitial mastitis*—
Primolut-N (nor-ethisterone): 5 mg. tablets b d from the 18th to the 25th day of the cycle.

Dosage *Chronic cystic mastitis*—
Primolut-N (nor-ethisterone): 5 mg tablets t d s from the 15th *to the 25th day of the cycle.*

Note: The failure to obtain regression in an affected site, particularly where other lesions have regressed, calls for reconsideration of the diagnosis and immediate repetition of steps directed at the exclusion of malignancy

MAMMARY CANCER

In the treatment of mammary cancer it must be borne in mind that the final prognosis is in no way altered by application of *endocrine therapy. In the appropriate cases, however,* considerable extension of useful existence, objective improvement in

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* Atkins, H

† Cuningham and Lang *Med J Aust* Sept 14th, 1962

metastatic sites, alleviation of pain and general physical and psychic improvement can be achieved, but the eventual progression of primary or secondary foci will only be temporarily reversed or delayed. Hormone therapy together with general supportive measures is usually secondary to surgery and/or radiotherapy directed at local and metastatic lesions In inoperable cases involving widespread metastases hormone therapy alone may be employed in conjunction with general supportive measures. While it has never been demonstrated that endocrine substances are carcinogenic in humans, there is distinct evidence that certain forms of mammary carcinoma are exacerbated by some hormones and for endocrine purposes malignant changes in the breast may be divided into three groups·

1 Oestrogen accelerated.
2. Pituitary accelerated
3 Independent of hormonal influence

Treatment

Hormone therapy may take two forms—(a) ablative destruction of endocrine glands, (b) administration of hormones—and is usually undertaken in progressive phases In order that the maximum extension of useful existence can be obtained, it is generally recommended that each phase be used to its fullest extent with the subsequent step being adopted only when further deteri oration is noted, but more than one phase may be adopted simultaneously Unfortunately the selection of cases that might be responsive to hormone therapy and the further selection of the appropriate type of hormone therapy is difficult and no simple means exists, other than trial methods

1 Oestrogen Accelerated

This type occurs principally in the younger age group, i e the premenopausal patient and up to 5 years postmenopause

Phase 1: Oophorectomy—it has been well established that removal of the major source of oestrogen production by means of surgical castration may often produce long-term remissions in the premenopausal patient The argument for oophorectomy, as a first step in premenopausal patients without recognisable secon-

daries, is strongly supported by definite evidence* that in a certain group of patients the occurrence of a natural menopause leads to a remarkably lengthened latent period before the appearance of metastatic lesions. Failure of this procedure to induce subjective or objective improvement would indicate that the lesion is not oestrogen accelerated and is therefore either independent of hormone influence or dependent on pituitary factors. Where castration produces improvement or arrest of deterioration, phase 2 may be applied either concurrently or at the first sign of further regression.

Phase 2: Androgen Therapy—An androgen test may sometimes be of value as a means of indicating whether castration with androgen therapy is an appropriate course of action For this purpose trial usage of testosterone propionate (Testoviron) in a high dosage is preferred. For therapeutic measures the standard recommended dose of 1,000 mg. testosterone propionate or its equivalent per month is best carried out with Primoteston-Depot (testosterone oenanthate) which combines twice the potency of testosterone propionate with a marked duration of effect. In the castrated female the use of androgens is directed at limiting the effect of adrenal oestrogens whereas in the patient who has not been previously castrated, this therapy will suppress ovarian oestrogen production and directly antagonise the local effect of oestrogens on breast tissues At the same time, general improvement is ensured by way of marked stimulus to protein anabolism and psyche

Dosage Primoteston-Depot. 250 mg 1 c c ampoule i m given every 14 days

Response is usually rapid and if desired the dosage may be increased but must never be reduced nor must the therapy be interrupted. It is natural on a dosage such as this that side effects may be expected in the form of virilisation and oedema as set out in the section dealing with androgens in the female.

Note. *The use of methyl testosterone has at times been suggested* but it is considered to be somewhat unreliable because its metabolism is not fully known and no increase of 17-ketosteroids can be demonstrated Similarly the use of so called "non virilising

* *J.A.M.A.*, 172 1271 1960

androgens" is sometimes suggested but it should be recognised that these are invariably weak androgens and when applied to mammary carcinoma at an effective dosage level will produce virilising effects equally severe as those stemming from the more potent androgenic substances. The use of these weaker androgens is only acceptable when they carry potent anabolic effects (protein anabolic agents) and then only as an adjunct to the standard therapy and only those substances which are not metabolised to *oestrogenic forms should be used.*

Phase 3: Andrenalectomy—Patients with oestrogen accelerated mammary cancer, who no longer respond to androgen therapy, should respond well to bilateral adrenalectomy, since this procedure removes a further site of oestrogen production. Following bilateral adrenalectomy it is essential that patients be maintained on replacement of corticoids and it is equally essential that the corticoids used possess a mineralocorticoid effect, for example cortisone acetate (Scheroson), cortisone oenanthate (Scheroson-Depot) or hydrocortisone acetate (Scheroson F). Cortisone derivatives such as Prednisone, Prednisolone etc. which are essentially glucocorticoids must not be employed as a replacement therapy

Phase 4: Hypophysectomy—This is the final stage of hormone therapy in the oestrogen accelerated group and is sometimes applied when all other phases have finally failed to arrest the progress of the disease It has been shown that the results of treatment with hypophysectomy alone are virtually identical with those achieved by adrenalectomy alone * However, there is distinct evidence† that response to castration or perhaps even androgen therapy alone, is indicative of a more likely response to hypophysectomy

2. Pituitary Accelerated

The precise nature of the pituitary factors which contribute towards the acceleration of certain forms of mammary carcinoma is not clear However, it is thought that prolactin or growth hormone plays a role This type falls principally in the postmenopausal group but may also account for a certain percentage of patients in the premenopausal age group

* Joint Committee on Ablative Procedures, *J.A.M.A.*, Vol 175, No 9, p 787
† Ray *et al*, *American Journal of Surgery*, 90 344 1960

Treatment

Hypophysectomy by surgical techniques may be undertaken but it is more usual to attempt medical hypophysectomy by the use of administered oestrogens. Although oestrogens can be more effective than androgens in premenopausal patients, it must be emphasised that this therapy must not be undertaken until at least 5 years past the menopause unless the presence of an oestrogen accelerated form has been positively excluded.

Dosage *Stilboestrol: 15 to 30 mg. daily*

or

Primogyn-M (ethinyl oestradiol): *0·2 mg. tablets 3 to 5 times daily.*

With dosages of this nature side effects (nausea and vomiting, uterine haemorrhage, oedema, uterine prolapse) may be expected. Medical hypophysectomy may also be carried out by means of high dose androgens as outlined in phase 2. It has been shown* that androgens provide their greatest effect in the older age groups and although this is still not equivalent to the effects achieved with oestrogens, the concurrent stimulus to psyche and protein anabolism may warrant the selection of androgen therapy in certain cases

* *J.A.M.A.*, 182·1271 1960

MISCELLANEOUS INDICATIONS FOR HORMONE THERAPY IN THE FEMALE

ORAL CONTRACEPTION

Suppression of ovulation by the use of exogenous hormones has been known in principle and has been applied in clinical practice for many years. Theoretically any gonadal steroid or its derivatives, if sufficiently potent, can be employed but most substances either require repeated injection or produce side reactions, particularly menstrual irregularities, when used alone over long periods The advent of the nor-steroid substances provided progestogens that were sufficiently potent and well tolerated to enable ovulation to be suppressed by oral administration without disruption of cyclical menstruation. The application of these substances is based on the hormonal mechanism by which pituitary-ovarian activity is suppressed during pregnancy and although the precise mode of action has not been proven beyond doubt, it has been clearly demonstrated by endocrine assay that ovulation and subsequent corpus luteum function are suppressed and that this inhibition of activity is followed by immediate resurgence at cessation of dosage Some doubts still exist as to whether this is achieved by suppression of gonadotropin output or by mo[illegible]
but the l [illegible]
suppress[illegible]
terone acetate) the changes produced in the endometrium are sufficient in themselves to provide a logical explanation for prevention of pregnancy and it is likely therefore that a secondary mechanism also concurrently exists

The use of an appropriate progestational substance alone, whilst clinically effective, does not provide the same cycle control, presumably by virtue of the reduction in output of ovarian oestrogen Consequently additional oestrogen is incorporated This combined therapy may be broadly considered as one which suppresses the usual ovarian activity including ovulation, substitutes the normal endocrine req[illegible]
cal fashion reproduces a [illegible]
that is remarkably const[illegible]
this therapy in indicatior[illegible]
of the ovary tends to provide remissions for a high percentage of

patients in a wide range of indications. (See also dysmenorrhoea, menorrhagia, polymenorrhoea, oligomenorrhoea, endometriosis, mittelschmerz, bleeding at ovulation, etc.)

Dosage Anovlar (4 mg N.E.A. + 0·05 mg ethinyl oestradiol). 1 dragee daily. Treatment is commenced on the 5th day of a true menstrual bleeding and is continued for 20 days. Withdrawal bleeding should occur 2 to 4 days after cessation of the therapy

The reliability of this therapy as applied to control of fertility is verified by all investigators and is dependent solely on adherence to dosage directions. The therapy has undergone extensive investigations, all of which indicate that there are no irreversible effects nor has there been evidence of any latent undesirable effects, even when administered over long periods For more specific data see special brochure or the following references.

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ENDOMETRIOSIS

Endometriosis is a local lesion involving numerous organs but particularly those of the pelvis and arises from the development of ectopic endometrial tissues Although this aberrant tissue does not always respond to endocrine influence, it frequently follows the normal cyclical pattern of the uterine endothelium and by virtue of repeated bleeding and the incapsulation of the affected tissues, gives rise to the formation of cysts. Because of the "tarry" *nature of the contents these are described as "chocolate cysts" or* "blue dome" and "mulberry cysts". The incidence is relatively high and in particular appears to bear a relationship to social levels since it occurs much more frequently in the private patient than in the public patient

Causes

The aetiology of endometriosis is a subject of much debate but it may be assumed to be due to misplacement of endometrial cells by (a) transportation (lymphatic, venous, surgical, direct reflux menstruation) or (b) metaplasia of coleomic embryonic tissue Endometriosis occurs commonly in the myometrium and in this location is usually regarded separately under the classification of adenomyosis Other common sites are. the ovaries, fallopian tubes, cervix, ligaments of the uterus, vagina, rectum, recto-vaginal septum, urinary bladder. Although some 25% of endometriosis cases are asymptomatic, it frequently gives rise to secondary dysmenorrhoea, dyspareunia, mittelschmerz, menorrhagia, inflammations, general malaise etc It is also very commonly associated with infertility and is regarded as a causative factor in 25% of unexplained sterilities

Treatment

Treatment of endometriosis in the past has been primarily by

surgery but the advent of more recent endocrine techniques has provided an effective non-surgical alternative. The selection of technique depends principally on the age and parity of the patient.

1. *Surgical*—In the sexually mature female who does not desire further pregnancies, surgery may be radical in nature and extend to endocrine ablation as well as the removal of involved organs. This is the more usual procedure in the older age group but where preservation of reproductive function is necessary, palliative surgery may be adopted.

2. *Non-Surgical*—The use of progestogens to achieve regressive changes in aberrant endometrial tissue by means of "pseudo-pregnancy" was prompted by the remissions observed during normal pregnancy and the results of repeated pregnancies.*

This method which involves prolonged delay of menstruation has received the support of various workers† and satisfactory results have been demonstrated in 90% of patients with confirmed endometriosis after continuous administration of nor-ethisterone and nor-ethisterone acetate over periods ranging from 3 to 6 months

More recently it has been shown‡ that cyclical suppression of ovulation without interference with menstruation also provides outstanding relief of subjective symptoms together with regressive changes and softening of adnexal masses Using nor-ethisterone and nor-ethisterone acetate, remission of symptoms was achieved in 85% of patients and 6 months after cessation of therapy 67% were still relatively free from symptoms. Whilst slightly less efficacious than prolonged delay of menstruation for permanent relief of symptoms, this regime is decidedly cheaper and since it allows for regular menstruation, is psychologically less disturbing to the patient

Dosage *1 Prolonged delay of menstruation*—
Primolut-N (nor-ethisterone): 15 mg daily
or alternatively
Primolut-Nor (nor-ethisterone acetate) 10 mg daily

* Meigs *Obstetrics & Gynecology* 2 46 53 July, 1953
† Kistner, R W, *Amer J Obstetr Gynec* 75 2 264 1958
Greenblatt, R B, *J Amer Med Assoc* 166 12 1461 1958
Eliott and Hewson *A Symposium on Progestogens* The Women's Hospital, Crown St, Sydney, June, 1962
‡ *Grant, Alan Med J Aust*, 9 Dec, 1961.

The therapy is continuous over periods ranging from 3 to 9 months and it may be necessary at times to increase dosage slightly to prevent break-through bleeding A subsequent gradual reduction is often possible

Dosage 2. Cyclical regime—

Primolut-Nor (nor-ethisterone acetate): 5 to 10 mg. daily from the 5th to the 25th day of each cycle

or alternatively

Primolut-N (nor-ethisterone) 15 mg. daily from the 5th to the 25th day of each cycle In many cases it is possible to achieve equivalent results at even less cost by utilising nor-ethisterone acetate combined with oestrogen in the form of Anovlar (4 mg N.E A. + 0·05 mg ethinyl oestradiol): 1 dragee daily from 5th to 25th day of each cycle.

UTERINE FIBROID

Uterine fibroid or fibromata are benign tumours of muscle elements, fibrous tissue and blood vessels completely encapsulated by a fibrous, connective tissue capsule. They are subject to benign degeneration, descriptions of which can be found in any standard text-book on gynaecology.

Although they are the most common uterine tumour, fibromata rarely give rise to symptoms in the patient under 30 years of age They may be single or multiple tumours varying in size from millet seed to a size large enough to fill the entire abdominal cavity. They are classified, according to their location, as follows

1. *Submucous*—Fibromata just below the endometrium, encroaching on the uterine cavity and usually aggravating or causing menorrhagia, dysmenorrhoea and irregular uterine bleeding. These may also give rise to leucorrhoea

2. *Intramural*—Fibromata in the body of the uterus, when large, are most likely to be the cause of secondary dysmenorrhoea and menorrhagias

3. *Subserous*—Fibromata under the peritoneum cause no menstrual disturbance and are usually symptomless unless large

Treatment

Uterine fibromata are often symptomless, and unless large or rapidly growing are not generally grounds for surgery The menstrual function must be preserved in patients where possible, and

surgery but the advent of more recent endocrine techniques has provided an effective non-surgical alternative. The selection of technique depends principally on the age and parity of the patient

1. *Surgical*—In the sexually mature female who does not desire further pregnancies, surgery may be radical in nature and extend to endocrine ablation as well as the removal of involved organs This is the more usual procedure in the older age group but where preservation of reproductive function is necessary, palliative surgery may be adopted

2. *Non-Surgical*—The use of progestogens to achieve regressive changes in aberrant endometrial tissue by means of "pseudo-pregnancy" was prompted by the remissions observed during normal pregnancy and the results of repeated pregnancies.*

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Dosage 1. Prolonged delay of menstruation—
Primolut-N (nor-ethisterone). 15 mg daily
or alternatively
Primolut-Nor (nor-ethisterone acetate)· 10 mg daily

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* Meigs *Obstetrics & Gynecology* 2 46 55 July, 1953
† Kistner, R W, *Amer J Obstetr Gynec* 75 2 264 1958
Greenblatt R B, *J Amer Med Assoc* 166 12 1461 1958
Elliott and Hewson *A Symposium on Progestogens* The Women's Hospital, Crown St, Sydney, June, 1962
‡ Grant, Alan *Med J Aust* 9 Dec, 1961

Dosage Progynon Ointment (oestradiol): Topically 2 to 3 times daily.

oestrogen.

times daily over

In cases of premenstrual exacerbations, however, oestrogen would be contraindicated and treatment as in premenstrual tension syndrome could be instituted.

Dosage Primolut-N (nor-ethisterone). 5 mg. b d from the 18th to the 26th day.

SUPPRESSION OF LACTATION

If lactation must be suppressed quickly or its initiation prevented, such as in still-birth, it may be achieved by temporary suppression of the anterior pituitary. In the past oestrogens have been principally chosen but the use of these substances alone tends to be accompanied by local complications in the breast tissues The use of androgens either alone or in combination with oestrogens as well as exerting an influence on the pituitary, might be expected to produce regressive effects in breast tissues and would therefore appear preferable. The type of therapy applied varies according to whether or not lactation has been established.

1. To Prevent Establishment

Where it is known either prior to or at childbirth, that suppression of lactation is required, the immediate use of an oestrogen-androgen combination will provide marked inhibition of lactation

Dosage Primodian-Depot. i m. injection, 3 ampoules administered as one injection

This should be administered immediately post-partum in the case of still-birth but where the decision to suppress lactation is made prior to labour, better results are achieved if it is administered after the first stage.

2 Suppression of Established Lactation

Dosage Androgen Therapy—Testoviron (methyl testosterone) 5 mg tablets t d s for 2 days by buccal administration.

Alternative Dosage Oestrogen Therapy—Primogyn-C (ethinyl oestradiol) 0 02 mg A total of 50 tablets divided thus 9 tablets

particularly in those wanting future pregnancies Therefore, surgical treatment, where undertaken, is conservative and hysterectomy restricted to select cases Conservative therapy by irradiation or androgen treatment may be undertaken to bring about regression until the patient has reached the menopause, after which further regression takes place naturally, with the loss of oestrogen stimulation.

Specific Hormone Therapy—Androgens are administered to antagonise follicular hormone stimulation, thereby causing regression of the tumour and symptoms; in particular, uterine bleedings.

Dosage Primoteston-Depot (testosterone oenanthate): *100 to 150 mg every 3 to 4 weeks or on the 14th day of the menstrual cycle.*

Therapy is continuous (unless surgery is indicated or signs of virilisation occur) until definite regression is achieved or the patient reaches the menopause

Side effects are minimal. Virilisation may occur in a small number of patients, in which case therapy is stopped for several months to allow for reversal of virilisation. This reversal should be complete except for vocal changes.

Bleeding from Fibroids

Although endocrine therapy is not expected to influence bleeding arising from pathological lesions, bleeding which stems from fibroids is a rare exception. The use of hormones cannot be expected to *influence the course of the fibroids or reduce the frequency of menstrual symptoms in this dosage but it can be employed to control associated haemorrhage until such time as more appropriate action can be taken.*

Dosage Testoluton Forte (*ampoules containing 25 mg. testosterone propionate + 10 mg progesterone*): *i m. injection daily for 3 days during menstruation.*

ACNE JUVENALIS AND VULGARIS

In cases where relative excess of androgens is suspect as a cause of increased sebaceous activity, this condition has been treated successfully with oestrogen Concurrent application of a regime directed at improved facial hygiene and the eradication of infection should be employed

with buccal or sub-lingual administration of Testoviron (methyl testosterone) tablets or with Primoteston-Depot (testosterone oenanthate) i m injection for a period of approximately two months per course of treatment.

d the prac-
'oided dur-

Dosage Testoviron (methyl testosterone): 10 mg. tablets once daily for 1 month or 5 mg daily for 2 months by buccal administration

or

Primoteston-Depot (testosterone oenanthate) 100 mg. i m. injection (early in the menstrual cycle or every 3 to 4 weeks)

on days 1 and 2, 8 tablets on days 3 and 4, and 7 tablets on days 5 and 6; or 2 tablets four hourly.

FRIGIDITY

Frigidity is defined as lack of orgasm rather than a lack of libido, although one may give rise to the other. It is very common in the young newly married patient, but becomes a medical problem only when persisting or when the onset is secondary to psychic disturbances or pelvic pathology in the previously sexually well adjusted patient.

Causes

Frigidity may be broadly classified into two forms: (a) pseudo-frigidity, (b) true frigidity according to the nature of the primary cause

1. *Pseudo-frigidity*—This might arise from organic diseases which lead to dyspareunia—faulty male technique, male incapacity, environmental factors, fear of pregnancy Fear of pregnancy, however, often is used as a cover for more deep-seated sexual difficulties.

2 *True Frigidity*—True frigidity is a deep-seated psycho sexual problem which may have its primary origin in some psychic factor or may develop secondary to continuation of the factors underlying pseudo-frigidity It may range from an incapacity to achieve orgasm despite normal or even exaggerated libido through increasing grades of sexual anaesthesia to complete revulsion coupled with defence mechanism (vaginismus, etc)

Treatment

The most important factor in the treatment of frigidity is the removal or correction of the underlying causes This may be supported by the use of hormone therapy in which the effects of androgens are employed The rationale for the use of androgens is based on the capacity to increase clitoral size and sensitivity and to produce stimulation of libido

Androgen therapy may be administered in one of several forms The topical application directly to clitoris has been advocated, but is generally unacceptable to the patient and does not give the libido increase required The most satisfactory application is

sexual maturity, is now the first function lost. This results in anovulatory disturbances which give rise to typical excessive or

(a) Follicular hyperfunction resulting in hyperhormonal amenorrhoea and subsequent metropathia haemorrhagica
(b) Luteal insufficiencies resulting in oligomenorrhoea, premenstrual syndrome, menorrhagias.

Treatment for these indications is dealt with elsewhere under the respective headings

2. Menopausal Phase

With continued atresia of the ovaries there is a further progression of total loss of ovarian response. As a result of the concomitant loss of oestrogen effects, menstruation ceases and there is a loss of pituitary inhibition as demonstrated by increased activity, particularly in the basophils which increase in size (castration cells) and output of, principally, F S.H. This phase is consequently classified as a hypergonadotropic phase and the increase in excreted gonadotropins remains apparent for several years after the menopause * That the increased pituitary function is not necessarily limited to gonadotropins is not uncommonly reflected in signs of increased adrenal activity at this stage (facial hirsuties, osteoporosis). As well as the loss of menstruation a classical syndrome of vasomotor and psychic disturbances (fatigue, headache, insomnia, palpitations, night sweating, hot flushes, over-excitability, depression) is common to approximately 80% of all women These symptoms are again similar to, but much more severe, than those experienced during the corresponding phase of the menarche.

While it is established that a definite relationship exists between the loss of ovarian function and the occurrence of these symptoms, the pathway by which they are induced is not clear. Apart from the fact that gonadotropins do not appear to directly influence tissues other than those of the gonads, other arguments also render elevated gonadotropins unacceptable as a direct cause It has, for instance, been shown that alleviation of symptoms with

* Loraine, J A, *Clinical Application of Hormone Assay*, E & S Livingstone, London (1958)

HORMONE THERAPY IN MENOPAUSE AND POSTMENOPAUSAL CONDITIONS

MENOPAUSE

The involution of the ovary at the end of the reproductive phase of life is a gradual and normal process, but one which generally gives rise to a procession of symptoms which sometimes appear unrelated to endocrine disturbances. A better understanding of the relationship between these symptoms and endocrine function is achieved if menopause is considered as a continuous process that may be divided into three main phases:

1. Premenopause. 2 Menopause. 3. Postmenopause or senescence

Causes

This loss of ovarian function is a normal physiological process occurring principally between the 45th and 50th year of life. It can, however, be induced prematurely by castration or irradiation and would also appear to be a common sequela to hysterectomy even though the ovaries themselves remain intact. In other than ablative causes the precipitation factors remain obscure and presumably result from natural ageing processes. There is an acceleration of atrophic changes associated with loss of ovarian weight, and increased growth of fibrous tissue in both the medulla and the cortex accompanied by sclerotic changes in the vascular supply The primordial follicles, although substantially reduced, still exist (at 45 years, approximately 8,000 per ovary) and numbers still remain subsequent to actual cessation of menstruation, but eventually only corpora albicantia or fibrotic corporae remain. Although there is also continued excretion of oestrogens at a reduced level, it might be assumed that this is principally of adrenal origin The progressive phases of the climacteric represent a reversal of the sequence observed at the menarche and each phase is allied with symptoms which are typical for that particular phase in both transitional periods·

1. Premenopausal Phase

Due to the changes that occur in the ovaries there is a loss of normal ovarian response to pituitary gonadotropins and regular ovulation, which is the last event achieved at the beginning of

weeks to 1 or ½ tablet per day; to be swallowed whole to retain the optimal balance of activity in the dosage.

3. Postmenopausal Phase (Senescence)

With the loss of ovarian oestrogen the levels circulating from adrenal production are insufficient to maintain the normal genital and extragenital effects As a result, there is regression and atrophy in all genital tissues together with vascular and metabolic changes. Hormone therapy therefore has an application in numerous senile indications related to hormone deficiency states:

(a) Osteoporosis.
(b) Senile vaginitis.
(c) Senile pruritus—vulvae et ani
(d) Peripheral circulatory disturbances, e g, acro-cyanosis, dead fingers, intermittent claudication, psychoses of the elderly due to poor circulation in the brain.
(e) Senile diabetes
(f) Senile skin conditions, e g, keratodermia climactericum (thickening of soles and palms)
(g) Endocrine arthropathies

OSTEOPOROSIS

Osteoporosis is the most common form of bone "disease" and affects such sites as the vertebral column, pelvis and (to a lesser extent) femur. The highest incidence of osteoporosis of functional origin is generally found in postmenopausal females In fact 40% of women past 65 years show radiological signs and at least 10% clinical signs of this condition In the past osteoporosis has been divided into two stages—menopausal and senile However, these are now considered to be the same

Causes

Functional

1 Deficiency of sexual hormone production In this condition bone destruction by osteoclasts is normal, but replacement by osteoblasts, i e. the laying down of new bone matrix of protein origin and taking into the matrix materials such as calcium and phosphorus salts, is depressed because there is no stimulation by sex hormones and normal physical activity

2 Due to inactivity In bedridden patients or those immobilised by fractures there will be a loss of bone substance due to depressed osteoblast activity

androgens is not associated with a decrease in gonadotropins; increased gonadotropins in primary hypogonadism is not associated with menopausal symptoms; menopausal symptoms are not common to all menopausal women, whereas elevated gonadotropins invariably are. It has therefore been suggested and more generally accepted that deficiency in oestrogens is the principal factor and while this may be true in so far as a primary cause is concerned, it is not acceptable as the general cause since similar remission from symptoms can be successfully achieved by the administration of androgens, and, in fact, some of the more potent progestogens, particularly those recognised to possess a central action.

It would therefore appear more reasonable to assume that the mechanism by which the total loss of ovarian steroid production causes the systemic reactions arises from a reflex disturbance of other centres by the hypothalamus as its activity is increased by the exaggerated feedback stimulus

Treatment

Therapy is aimed at reduction of hypothalamic activity and thereby the removal of reflex disturbance to the centre of psyche and the vegetative nervous centre. It is basically an oestrogen replacement therapy, but oestrogen therapy alone has several disadvantages: (a) Proliferation of endometrium and possible uterine bleeding. (b) Weak stimulation of psyche. (c) Tension in the breast.

These may be offset by combining oestrogen with testosterone, since testosterone antagonises oestrogenic effects on the endometrium and breast and gives a strong stimulation to psyche An optimally balanced oestrogen-androgen therapy achieves:

(a) Strong suppression of hyperfunction in the anterior pituitary (b) Strong stimulation to psyche (c) No proliferation of endometrium and therefore no uterine bleedings from the treatment.

Dosage Primodian-Depot (65 mg testosterone—in the form of oenanthate + oestradiol valerianate 4 mg): 1 c c. i.m injection every 3 to 4 weeks to commence, then extending the period between injections

Oral Alternative·

Dosage Primodian Tablets (4 mg methyl testosterone + 0·002 mg ethinyl oestradiol). 4 to 6 tablets daily, reducing after 3

2 Rich protein diet is essential, but it is not necessary to give calcium as in other bone disease

3. Physiotherapy is indicated to put stress on affected bones and to stimulate osteoblast activity.

Subjective improvement is rapid, giving relief of pain and increased wellbeing. Objectively, however, radiological improvement is extremely slow, if at all

SENILE VAGINITIS

Senile vaginitis occurs when, due to oestrogen lack, the senile atrophic epithelium loses the normal protection of the proliferation of cornified squamous epithelium and Doderlein bacillus action, which gives an acid medium so inhibiting pathogen activity. Oestrogen restores the normal proliferation of vaginal epithelium.

Treatment

Replacement by oestrogen therapy

Dosage (a) Primogyn C (ethinyl oestradiol) 0 02 mg 1 to 2 tablets daily.

(b) Progynon (oestradiol) Ointment locally, usually by use of tampon administration.

KRAUROSIS VULVAE

Kraurosis vulvae requires oestrogen therapy as in senile vaginitis to bring about proliferation of healthy tissue, improvement in blood supply and reduction of secondary infection, etc. Dosages as for senile vaginitis.

SENILE PRURITUS

Senile pruritus—vulvae et ani are atrophic skin conditions with low grade secondary infection causing itching of the vulvae and anus

Treatment

Oestrogen replacement therapy

Dosage Progynon (oestradiol) Ointment topically

plus

Primogyn-C (ethinyl oestradiol)· 0 02 mg 1 to 2 tablets daily until condition is relieved

or

Prednisolone topically—Scheriproct Ointment

Induced Causes and Pathology

1. Corticoid induced catabolism. Bone destruction by the cortisone catabolic action is high in long-term cortisone therapy. Tumours, etc., of the suprarenals, which also give high cortisol levels, will produce osteoporosis as part of Cushing's syndrome.

2. Pathological—tumours of the parathyroid and adrenal cortex; hyperthyroidism.

3. Faulty nutrition.

Symptoms

Pain in the bones, particularly back pain, low back pain radiating down over the buttocks, etc., are common. Shortening of torso and appearance of a transverse fold at the navel and kyphotic (hunched) appearance are late signs, as are deformities of bone and spontaneous fractures.

Patients usually have a thin, dry skin, asthenia and occasional anorexia are also noted.

Diagnosis

1 Radiological examination

2. Calcium, inorganic phosphorus and serum alkaline phosphatase levels are normal when the causes are non-pathological.

Treatment

1. *Sex hormone therapy—oestrogen for its strong protein anabolic* effect in bone and mineral retention, plus testosterone for its synergistic effect in these points. The androgen action in antagonising oestrogen genital effects avoids the complication of uterine bleeding and breast pain

Dosage Primodian-Depot· i.m. at 3 weekly intervals

or

Primodian Tablets. 3 to 4 per day Treatment is continuous

Alternative Dosage

The development of steroids capable of producing marked retention of protein and minerals provides an effective alternative to the above therapies.

Dosage Primobolan-Depot (methyl androstenolone oenanthate) 100 mg. i m fortnightly

or

Primobolan Tablets (methyl androstenolone acetate) 5 mg tablets q i d. for commencement, 5 mg. b d as a maintenance therapy

HORMONE THERAPY IN THE MALE

HYPOGENITALISM AND EUNUCHOIDISM

The absence of mature sexual development in the male is classified as hypogenitalism. Where the condition develops in the mature male, gradual regression in the genitalia usually occurs coupled with loss of function, but secondary sex characteristics may not be markedly affected unless there is a source of excessive oestrogen production Where changes of secondary sex characteristics are also involved the term "feminisation" is usually applied. Where the onset is prepubertal, however, there is sexual infantilism with associated failure in the development of secondary sex characteristics and the specific term eunuchoidism is generally applied.

Causes

1 *Non-Endocrine*—Congenital absence of genitalia or acquired anatomical defects in the form of castration or testicular damage *lead to hypogenitalism. Systemic factors should always be considered*, but apart from intoxications these do not appear to be a common cause. Psychogenic factors are common causes of disturbance but are associated solely with a loss of sexual capacity.

2. *Endocrine*—Excessive endogenous production of oestrogens, such as may arise from certain tumours of the testes or adrenal cortex, if sufficiently high, lead to regressive changes classified as "feminisation" (see p. 45)

3 *Functional*—Functional hypogenitalism might be divided into *two forms according to the site of interference, namely* hypogonadotropic or hypogonadal

(a) Hypothalamic Level Apart from rare neurogenic interference arising from intracranial lesions (Fröhlich's syndrome) this level is an unlikely site for a primary disturbance

(b) Pituitary Level Primary pituitary deficiency is a relatively likely and intractable factor, usually arising from marked disturbances (trauma, tumours etc) and frequently ex*tends to panhypopituitarism The result of generalised loss* of anterior pituitary function is reflected in organs other than the gonads as in pituitary dwarfism etc A selective

PERIPHERAL CIRCULATORY DISTURBANCES

These conditions, common in the postmenopausal female, are related to the deficiency of oestrogen and its stimulation of peripheral circulation (vasodilatory effect). The use of replacement therapy is therefore rational and as well as the therapies listed below, Praenitron (Schering A.G.) is also recommended to increase this vasodilatory effect:

Dosages (a) Acro-cyanosis—cyanosis of the extremities
Primogyn-C (ethinyl oestradiol): 0·02 mg. tablets. 1 to 2 daily
or
Primodian Tablets: 2 to 3 tablets daily.

(b) Dead fingers—therapy as in acro-cyanosis
plus
Progynon (oestradiol) Ointment topically.

(c) Intermittent claudication—intermittent limping from painful arteroid spasm and muscular cramps
Primodian-Depot: every 3 to 4 weeks

KERATODERMIA CLIMACTERICUM
(Haxhausen's Syndrome)

Dosage Primodian-Depot: every 3 to 4 weeks.

ENDOCRINE ARTHROPATHIES

Dosage Primodian-Depot: every 3 to 4 weeks.

FEMALE PROTEIN DEFICIENCY STATES

Dosage Primobolan-Depot (methyl androstenolone oenanthate): 100 mg i.m. fortnightly
or
Primobolan Tablets (methyl androstenolone acetate): 5 mg tablets q i d. for commencement of treatment, reducing to 5 mg b d as a maintenance therapy

Dosage Testoviron (testosterone propionate): 10 mg i m every 2 to 3 days until satisfactory improvement is noted

Alternative Dosage Primoteston-Depot (testosterone oenanthate) 100 mg i m. every 3 weeks

PROSTATIC CARCINOMA

This malignant growth of the prostatic glandular tissue is a slowly progressing condition Apart from the original site, secondary metastases are likely to occur in other pelvic organs (particularly the urinary bladder) and in the bone structure of the pelvis and femur

Treatment

Hormone therapy is usually secondary to surgery directed at primary and metastatic lesions. Malignant new growth is dependent upon testosterone stimulation Castration was therefore found beneficial, but since this would only account for approximately one-half of the androgen production, a better effect is obtained by medical castration (or medical hypophysectomy) with high doses of oestrogen. This has three effects.

(a) Inhibition or suppression of anterior pituitary and consequently elimination of gonadotropins and gonadal androgens

(b) An antagonism of testosterone effect on prostatic glandular tissues

(c) Stimulation of unaffected prostatic interstitial tissue

[illegible] ol): 0 2 mg commencing [illegible] to a maintenance of 1 to [illegible] s equal to approximately 5 mg. of stilboestrol and has the further advantages that it is better tolerated (less nausea) and that it provides stimulus to the psyche.

Side Effects—It is to be expected that if a high dosage is maintained for a lengthy period, signs of feminisation (impotence, pain and swelling of the breast, etc) will occur

MALE CLIMACTERIC SYNDROME

The loss of testicular function in the male with the accompanying loss of testosterone production gives rise to a gradual loss of androgen effects throughout the body Although the transition from sexual maturity to senescence in the male is much more

2. Oligospermia

Depending on the severity, prospects of improvement in this group are better and although results are variable, two therapies are considered as worth while in these cases.

Stimulation Therapy: *The use of gonadotropin therapy would appear to be of little value in those cases where the disorder arises from primary disturbances of the germinal tissues. However, in those cases where pituitary hypofunction is a contributing factor, direct stimulation of the gonads has been shown to provide improvement if the germinal epithelium is responsive.*

This may be achieved by two methods: (a) direct stimulation, (b) rebound stimulation.

(a) Direct *stimulation with* gametogenic type hormone (P.M.S.) *may be undertaken but it should be incorporated* with concurrent androgen therapy.

Dosage Primantron (P.M.S): 5,000 i.u. i m together with Testoviron (testosterone propionate): 10 mg. i m.

One injection of each substance is given every 3 days for a total of 10 injections per course and the course repeated after 2 months if necessary Dosages of less than 15,000 i u. *per week are considered to be of little value.*

(b) Rebound Stimulation: *Stimulation of the gonads may be attempted by methods aimed at increasing pituitary output and there is evidence that when the pituitary is suppressed and subsequently released, a rebound response occurs leading to increased gonadotropin output and improved spermatogenesis In this therapy androgens are employed in high dosage until such time as spermatogenesis is completely suppressed, in the hope that the "rebound effect" will lead to an improvement on pre treatment sperm levels* Response *to this therapy is variable but in view of the results which are sometimes achieved, it is generally considered that trial of this therapy is worth while in appropriate cases.*

Dosage *Primoteston-Depot (testosterone oenanthate). 250 mg* i m *every 10 days until spermatogenesis is suppressed.*

3. Asthenospermia

Since asthenospermia is most likely to be caused by lack of the nutritional energy giving factor (fructose), this condition should respond to low-dosage androgen therapy

and in those cases which do not respond to a trial therapy, it is likely that the problem has psychogenic basis While hormone therapy is principally employed as a substitution for testicular loss, it can also be used as an adjunct to psychotherapy in order to increase libido

Dosage Primoteston-Depot (testosterone oenanthate) 100-200 mg i m. every 2 to 4 weeks, according to severity.

JUVENILE ACNE–MALE

*This is a skin condition peculiar to juveniles. It is generally con*sidered to be due to a large and variable amount of testosterone (since it is sometimes a side effect of testosterone therapy). It *takes the form of eruptions that are often followed by disfiguring* keloid formation.

Treatment

Oestrogen therapy is undertaken to antagonise the effect of testosterone on the skin.

Dosage Progynon Ointment (oestradiol): 2 to 3 times daily supported by

Primogyn-C (ethinyl oestradiol): 0 02 mg twice daily.

PROTEIN DEFICIENCY STATES–CACHEXIA

In these conditions (and following long and exhausting illness) the protein anabolic effect of androgens may be utilised effectively

Dosage Primoteston-Depot (testosterone oenanthate) 100 to 250 mg i.m every 2 to 4 weeks

or

Primobolan-Depot (methenolone oenanthate) 100 mg i m every 2 to 4 weeks

OSTEOPOROSIS AND SLOW HEALING FRACTURES

Osteoporosis occurs less frequently in the male than in the female and is manifest much later It may appear earlier in younger males who show definite clinical symptoms of androgen deficiency states.

Treatment

As in females, the combination of oestrogen and androgen is used in order to take advantage of synergistic action of both hormones in bone metabolism.

gradual than in the female, a climacteric as such is acknowledged and the loss of function is characterised by the following symptoms:

1. Mental and physical fatigue including.
   - Loss of concentration;
   - Poor memory;
   - Depressions (mental) with loss of confidence;
   - Physical weakness;
   - Impotence.
2. Pseudo-anginal attacks.
3. Vague muscular pains, etc.

Treatment

Treatment of the male climacteric is by replacement therapy as would normally be applied where these symptoms are produced by castration.

Dosage Primoteston-Depot (testosterone oenanthate): 100-250 mg. i.m. every 2 to 4 weeks according to severity. Failure to respond to this therapy would indicate the absence of a testicular deficiency.

IMPOTENCE

Impotence is an extremely common complaint and occurs to some degree in 40% of married men. Impotence may vary widely in the degree of severity and ranges from absence of libido to *inability to obtain or sustain an erection*. *Inability to ejaculate* and premature ejaculation may also be classified under the heading of impotence.

Causes

The causes of impotence are numerous and due regard should be given to all aspects before undertaking endocrine therapy. Where impotence is acquired after previous normality, organic or depressive factors may be suspected. Where impotence varies according to circumstances or has been present throughout life in the otherwise normal male, psychogenic factors are the principal cause. Psychogenic types may be further subdivided into simple forms *developing from simple failures, fatigue, boredom,* or more deep-seated psycho-sexual difficulties.

Treatment

Successful treatment by endocrine therapy is dependent upon elimination of factors not associated with testicular deficiency

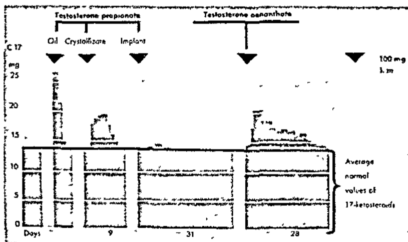
MODES OF ADMINISTRATION

The importance of correct dosage and timing has been stressed in preceding sections, and in order that desired results may be best achieved, consideration must be given to the type of hormonal preparation used and the route by which it is administered

There is a marked variation in intensity, duration of action and speed of onset associated with different modes of administration.

However, consistent effects can be expected with steroid hormones, and standardisation in terms of milligrams permits a comparison of potency and the establishment of reliable dosage schedules irrespective of which preparation is used (see table 1)

Although oral or parenteral administration is now given preference, numerous routes have been utilised by which to introduce hormones into the body. They have been administered perbuccally, perlingually, per vaginum and even per rectum As well as being implanted they have been injected intramuscularly, and in some cases intravenously.



Duration of action of various testosterone preparations as shown by the excretion picture Duration of excretion corresponds to clinical observation After J Bauer *Med Klin* 49, 42 1677 1954

Dosage Primodian-Depot: i.m every 2 weeks (see also Osteoporosis in the Female)

or

Primobolan-Depot (methenolone oenanthate): i.m. every 2 weeks.

Peroral: While this is the most convenient form, there is some limitation to achievement of full effect as certain hormones are partially or wholly destroyed in the gut or inactivated in the liver. Ethinyl oestradiol, ethisterone and nor-ethisterone are completely effective by mouth, while methyl testosterone is approximately 50% effective.

Buccal: Inactivation can be avoided by absorption through the buccal mucosa of the canine fossa. This is similar to parenteral administration, since the hormone passes directly into venous circulation and reaches the target organ without traversing the gut or liver. Absorption from the canine fossa is optimal and preferable to other buccal sites, where the presence of a tablet might lead to increased salivation with consequent loss of activity of the hormone through swallowing.

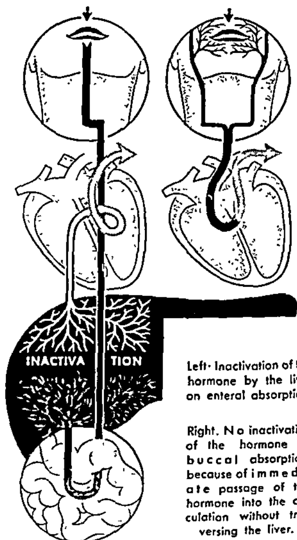
Transcutaneous: Inactivation is also avoided by the absorption through the more delicate skin areas (inner thigh and cubital fossa) of alcoholic solutions.

Intravenous: The intravenous injection of sex hormones is restricted mainly to specific circumstances where a speedy elevation of hormone levels is required, for example, in treatment of threatening abortion

Intramuscular: i m. injection, while giving a slightly slower onset of action, is the most common route of administration The most convenient method, particularly in lengthy therapies, is the use of hormone preparations that have a protracted effect

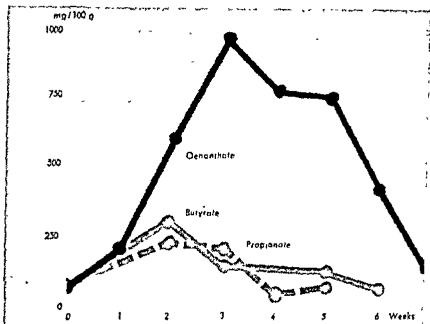
Crystalline Suspension: With crystalline suspensions the crystalline size governs the rate of absorption and therefore the duration of action The lack of standardisation of crystalline size in commercial products, plus the limits imposed by needle bore, introduces marked variations in effect. The results from emulsified forms are even more unreliable

Depot Hormones: The use of fatty acids to produce esters of the various hormones results in increased potency as well as prolongation of action, thought to be achieved in some esters by the slow saponification and release of free hormone within the body, whilst in others this "depot" action is probably effected by delayed absorption, utilisation and degradation The benzoic and proprionic esters, while not regarded as having "depot" action, extend the hormonal effect over several days.


Administration
Oral
Buccal
INACTIVA
TION
Left· Inactivation of the hormone by the liver on enteral absorption
Right. No inactivation of the hormone on buccal absorption, because of immediate passage of the hormone into the circulation without traversing the liver.

Constant levels of release over longer periods are achieved by combining steroids with the long-chain fatty acids (oenanthic, valerianic and capronic), and these hormone preparations carry many advantages over implants or crystalline suspensions. They are not foreign to the body and by virtue of their high solubility in well tolerated oils, facilitate lengthy or high dosage therapies. The intensification and prolongation of their action is dependent on their chemical composition, and is therefore constant and standardisation is possible.

Hormone Pellets for Implantation: The subcutaneous or better still subfacial implantation of sterile tablets was the first means of achieving prolonged action. This method has now been generally discarded. Such possible factors as encapsulation or extrusion and diminished absorption as the surface area of the pellet is reduced, render this application unreliable. Furthermore, where a continuous, high level of the hormone is required, such as in the progestogen therapy for habitual abortion, the rate of absorption using this method would be too low to achieve a required therapeutic response



Comparison of effects of fatty acid esters of testosterone on the seminal vesicle weight of castrated rats, after one subcutaneous injection of 20 mg in 0 4 c c sesame oil

After K Junkmann *Arch exper Pathol u Pharm* 215, 1/2 85, 1952

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TABLE 1

HORMONE	TRADE NAME AND SINGLE DOSE	ROUTE	PROLIF or SECR DOSE	RELATIVE POTENCY	DURATION IN DAYS
Oestradiol	PROGYNON 0.1 & 1 mg	ORAL	200 mg.	÷10	1
Oestradiol Benzoate	PROGYNON B OLEOSUM 1 mg 5 mg	I M	25 mg.	Standard	3-5
Ethinyl Oestradiol	PRIMOGYN-C 02 mg - ·05 mg. PRIMOGYN-M ·2 mg.	ORAL	2 mg	×10	1
Oestradiol Valerianate	PRIMOGYN DEPOT 10 mg	I M	10 20 mg.	×2	14
Progesterone	PROLUTON 5, 10, 25 mg	I M & I V.	250 mg	Standard	2
Ethisterone	PROLUTON C 5, 10, 25 mg	ORAL	1,000-2,000 mg	÷10	1
Nor Ethisterone	PRIMOLUT-N 5 mg	ORAL	150 200 mg	>1	1
Nor Ethisterone Acetate	PRIMOLUT NOR 2 mg	ORAL	60 mg	×3	1
Hydroxy Progesterone Capronate	PROLUTON-DEPOT 125-250 mg	I M	250 mg	>1	7 8
Testosterone Propionate	TESTOVIRON 5, 10, 25, 50, 100 mg	I M.		Standard	3 5
Testosterone Oenanthate	PRIMOTESTON-DEPOT 50, 100, 250 mg	I M.		×2	21
Methyl Testosterone	TESTOVIRON Buccal 5, 10, 25, 100 mg	BUCCAL		÷4	1

The following preparations are available in India under different trade names

	In India
DUOGYNON Simplex	DUOGYNON FORTE
PRIMANTRON	PRIANTIN
PRIMOGYN C	PROGYNON C
PRIMOGYN DEPOT	PROGYNON DEPOT
PRIMOTESTON DEPOT	TESTOVIRON DEPOT

The following preparations of M/s. Schering A. G. Berlin are not marketed in India

PRIMOBOLAN Tablets	PROGYNON ointment
PRIMOBOLAN DEPOT	PROLUTON 5 mg
PRIMOGYN M	PROLUTON C
PRIMOLUT – Nor	SCHERIPROCT ointment
PRIMOSISTON	TESTOLUTON
PROGYNON tablets 0 1 mg & 1 mg	TESTOLUTON forte

and TESTOVIRON tablets 100 mg